A STUDY ON SERUM MAGNESIUM AND ITS EFFECT ON MORTALITY AND MORBIDITY IN PATIENTS ADMITTED IN INTENSIVE MEDICAL CARE UNIT

AT

GOVT KILPAUK MEDICAL COLLEGE AND HOSPITAL, CHENNAI

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For the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

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BONAFIDE CERTIFICATE

This is to certify that the Thesis "**A Study on Serum Magnesium level and its effect on mortality and morbidity in patients admitted in intensive medical care unit at Govt Kilpauk Medical College Hospital, Chennai"** is a genuine work done by **Dr.M.SUMATHIRA**, Post Graduate Student in the Department of Medicine, Government Kilpauk Medical College under the guidance of PROF. DR. R. SABARATNAVEL M.D., Head of the Department, Department of Medicine, Kilpauk Medical College.

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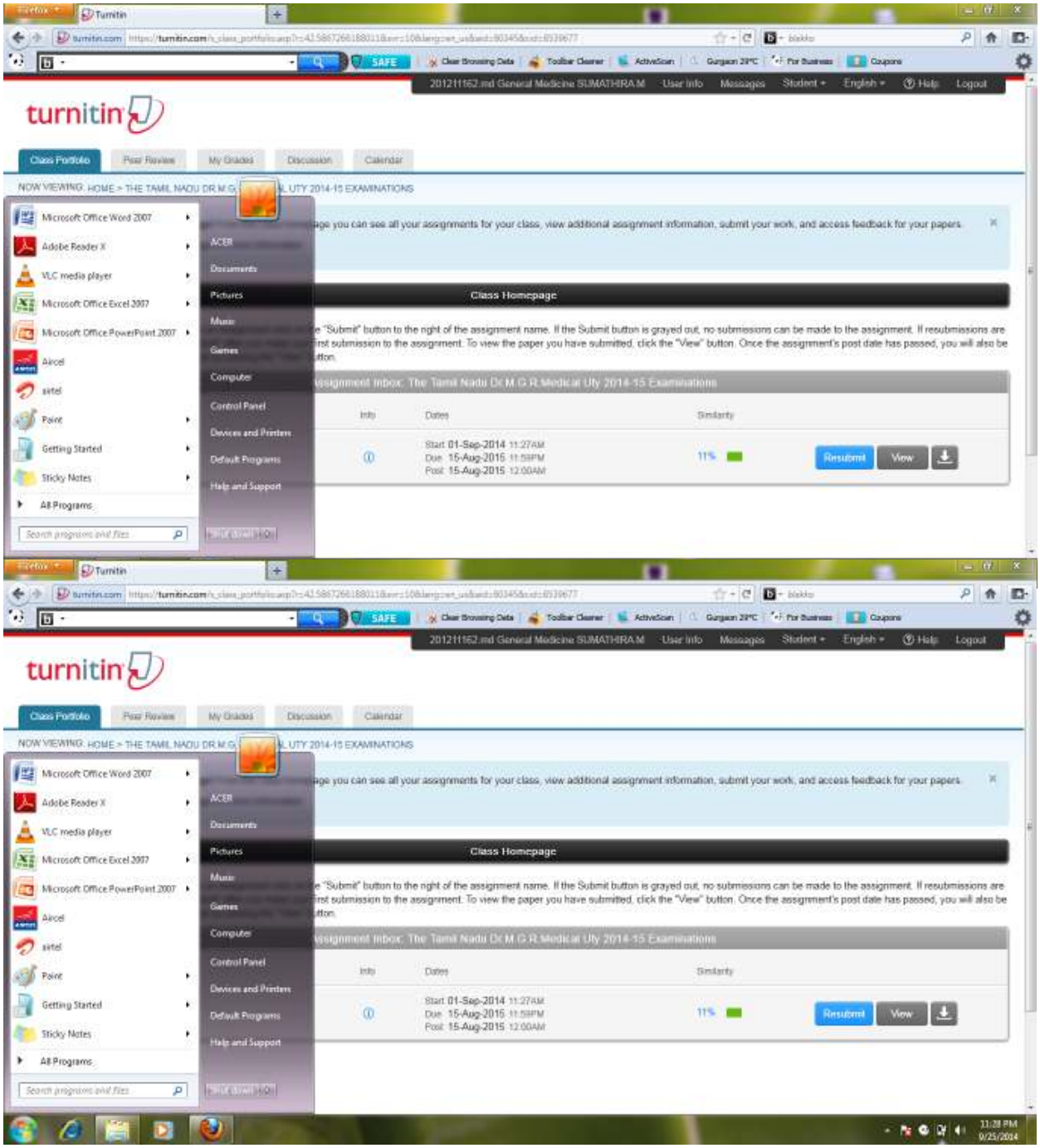
DECLARATION

I **Dr. M.SUMATHIRA** solemnly declare that the dissertation titled "**A STUDY ONSERUM MAGNESIUM LEVEL AND ITS EFFECT ON MORTALITY AND MORBIDITY IN PATIENTS ADMITTED IN INTENSIVE MEDICAL CARE UNIT AT GOVT KILPAUK MEDICAL COLLEGE AND HOSPITAL,CHENNAI"** has been prepared by me. This is submitted to the Tamil Nadu Dr. M.G.R. Medical University Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine)

Place: (Dr.M.Sumathira)

Date: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ABSTRACT

Background :

Hypomagnesemia is an important but under diagnosed electrolyte abnormality in critically ill patients at IMCU. There are many studies to find the prevalence of hypomagnesemia and its effects on mortality and morbidity in IMCU patients. This study was cross sectional study, carried out in IMCU patients at Kilpauk Medical College and Hospital, to study on serum magnesium level & its effect on mortality and morbidity

Aims and objectives:

To study serum magnesium levels in patients admitted in intensive medical care unit within 24 hours of admission and find out hypomagnesemia, to determine the associated outcome in terms of 1. Length of stay in IMCU, need for ventilator support, duration of ventilator support, mortality and APACHE II.

2. To assess the primary critical medical conditions associated with hypomagnesemia

3. To detect other electrolyte abnormalities associated with hypomagnesemia if any

Results:

In our study, 53% patients had hypomagnesemia , 47% had normal magnesium. Mean range of the APACHE score in the hypomagnesemic patients was higher (18.70 vs 10.09) , length of stay in ICU was longer(4.75 vs 3.5 days), need for ventilator support was higher (35.8% vs10.6%), associated with higher hypokalemia (39 % vs. 12 %), hypocalcemia (32 % vs. 8 %) and hyponatremia (45% vs 19%) . It was more frequent in sepsis and higher mortality rates were higher (30% vs 8.5 %). Duration of ventilator support did not have correlation with magnesium level.

Conclusion:

Hypomagnesemia has a higher prevalence among the Patients in IMCU set up and associated with higher APACHE score, longer stay in ICU, higher need of ventilatory support, higher mortality rates and higher electrolyte disturbances (hypokalemia, hypocalcemia , hyponatremia), are noted among these patients . It was predominantly present in sepsis. There was no correlation between hypomagnesium and duration of ventilator support.

INTRODUCTION

Magnesium is mainly seen in the intracellular fluid of all living cells and tissues and it is extremely essential for life. It is second most plentiful intracellular cation after potassium; fourth most plentiful after sodium, potassium and calcium in humans.

Magnesium plays a vital role in the transfer of energy and also storage, utilization of energy and it regulates as well as catalyzes >300 enzyme systems.[2]It acts as activator for many of the phosphate group transfer enzymes, for example, formation of ATP. It is found in certain enzymes, such as co-carboxylase. The enzymes needing magnesium are involved in intermediary metabolism, transcellular ion transport, muscle contraction, oxidative phosphorylation. Some examples are alkaline phosphatase, hexokinase, fructokinase, phophofructokinase, adenyl cyclase, cAMP dependent kinases, etc.

Mg is required for the formation of bones and teeth, maintains neuromuscular excitability, cardiac function and improves glucose tolerance by insulin dependent uptake of glucose, which is reduced in magnesium deficiency. Magnesium is attached to other nucleoside phosphates and nucleic acids and is needed for DNA synthesis.

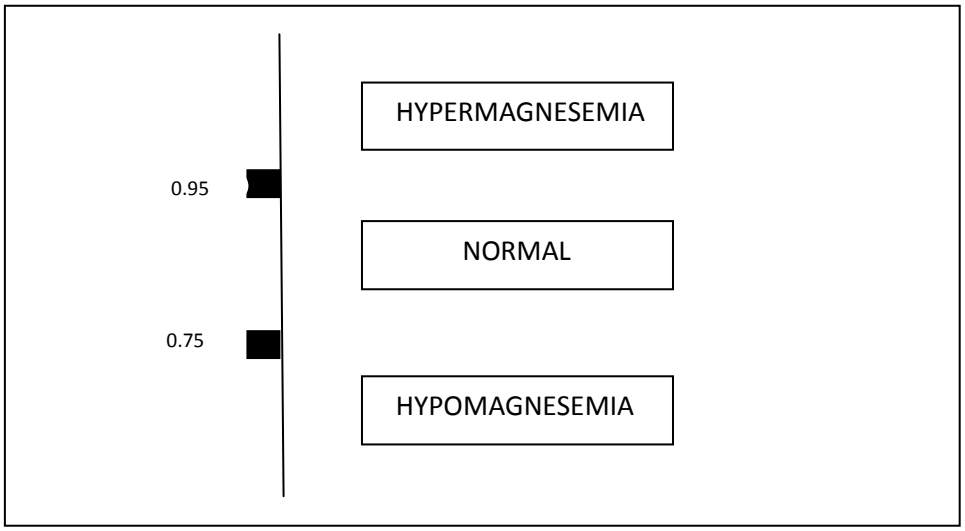
Hypomagnesemia has been expected to develop in 20% to 65% of critically ill patients during course of their stay in intensive care unit[1]. Though it is common, it is frequently under diagnosed abnormality in clinical practice and easily mistaken for potassium deficit.

Factors contributing to magnesium deficiency in critical care settings are reduced absorption due to altered gastrointestinal activity, malnutrition, renal loss of various drugs (e.g., digoxin and gentamicin also loop diuretics etc.), diabetic individuals, hypokalemia, hypocalcemia, poor content of magnesium in TPN solution.

Hypomagnesemia in critically ill patients has been found to have a higher APACHE II score and causes an increased requirement for ventilatory support as well as its duration because hypomagnesemia causes muscle weakness and respiratory failure which leads very much difficult to weaning the patient from the ventilator. Prolonged stay in Intensive medical care unit (IMCU) is also associated with higher mortality and morbidity. Hypomagnesemia contributes to cellular alteration associated with other electrolyte abnormalities. It aggravates the mortality and morbidity, and is found to be an important predictor of poor patient outcome in critically ill patients.

Normal range for total serum Magnesium concentration in mmol/L

(1 mmol/L=2mEq/L=2.43mg/dl)



Patients admitted with low magnesium levels in intensive care units can affect the prognosis of patients compared to those having normal levels of magnesium that is hypomagnesemic patients have a guarded prognosis. Hence in an IMCU set up, monitoring of serum magnesium levels along with other electrolytes has a very important therapeutic as well as prognostic implication.

Our study was intended to see the status of serum magnesium level in acutely ill patients, evaluate the association of magnesium level to various organ failure and duration of stay, electrolyte disturbance, requirement for ventilatory support, length of ventilatory support, mortality rate.

Also this study was undertaken to establish the value of the APACHE II score in determining the morbidity and mortality of acutely ill medical patients with hypomagnesemia admitted in intensive medical care unit (IMCU).

AIMS AND OBJECTIVES

1. To find out hypomagnesemia in patients admitted in intensive medical care unit within 24 hours of admission and to determine the associated outcome in terms of Length of stay in IMCU, need for ventilator support, duration of ventilator support, mortality, APACHE II.
2. To assess the primary critical medical conditions associated with hypomagnesemia
3. To detect other electrolyte abnormalities associated with hypomagnesemia if any

REVIEW OF LITERATURE:

Magnesium is a macro mineral, most essential for life, needed by body in large amounts. The average human body contains about 25 grams of magnesium. It acts as a part of the structure of the body because majority of magnesium is distributed in bone and functions as a cell regulator in chemical reactions throughout the body.

Magnesium disorders are common in critically ill patients in intensive care unit. Various prospective studies showed that 52.5% of hypomagnesemic and 13.5% of hypermagnesemic ICU patients were associated with higher mortality[3] .More than 80000 assays are being done every year in bigger institutions but there is controversy whether this is the best way to maximally benefit critically ill patients.

PHYSIOCHEMICAL PROPERTIES OF MAGNESIUM:

Magnesium belongs to group 2 element in periodic table having atomic mass of 24.305 Da and a Specific gravity of 1.738[4,5,6.] Magnesium binds water more than sodium, calcium and potassium.

The ionic radius of dehydrated Mg is small which explains its antagonistic behavior to calcium. Also magnesium cannot pass through narrow channels in biological membranes which can be passed by calcium.

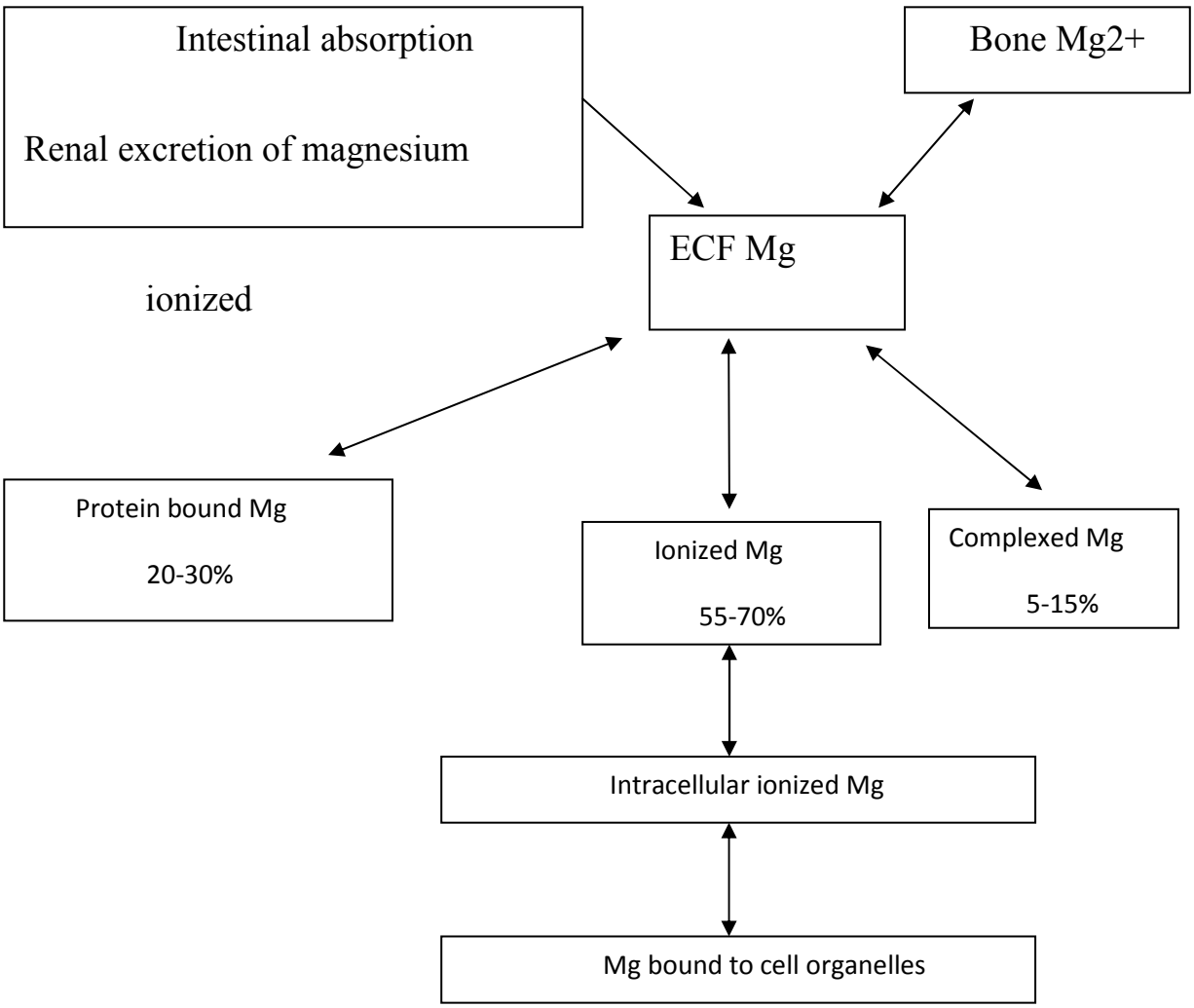
SOURCES OF MAGNESIUM:

Magnesium is widely distributed in vegetables, found in porphyry in group of chlorophyll of vegetable cells also in almost all animal tissues. Milk, eggs, cabbage, cauliflowers, fruits, cereals, beans, leafy vegetables and fish, nuts, almonds have particularly rich source and cheese, potatoes. Artificial foods and boiling, demineralised water contains low Mg content. Total Mg content in human body is 21 to 28g approximately or 20mmol/kg of fat free tissue.

DAILY REQUIREMENT OF MAGNESIUM:

In infants is around 100-150 mg, children-150-200 mg, in adult males 400mg, females 300mg, during pregnancy and lactation 450 mg[8,9].Doses above 600mg may cause diarrhoea.

MAGNESIUM HOMEOSTASIS:



Magnesium gets absorbed by intestine, stored in bones and excreted by kidneys. Intestinal absorption of magnesium is balanced against excretion of magnesium by kidneys[12]. Body depends on magnesium in bones to maintain serum levels constantly, when there is presence of magnesium deficit.

INTESTINAL ABSORPTION OF MAGNESIUM

It is absorbed by small intestine also from colon through a specific carrier system beginning within hour after consumption, follows at a steady rate for two to eight hours. In spite of intestinal absorption of dietary magnesium is about 30% to 50% approximately, when intake is low, the absorption rate is raised to 80%. Plasma concentration of magnesium in healthy individual is about 0.65-1.05mmol/L, while shortage of magnesium which is compensated by stored magnesium in bone and muscle.

ABSORPTION PATHWAYS:

Para cellular and transcellular pathways are the two pathways involved in Mg absorption. The former involves absorption via the small spaces within the epithelial cells. The latter involves active transfer of Mg through the epithelial cells which is subject to tight regulation.

Para cellular Mg transport in the epithelium of intestine occurs through unidentified claudins which occurring simultaneously with transcellular Mg transport through TRPM6 and TRPM7 apparent receptor potential channel melastatin group to increase Mg absorption.

Paracellular pathway involves claudin proteins and transcellular involves TRPM6, TRPM7 to increase absorption of magnesium. Para cellular pathway which is a passive one contributes to 80-90% of Mg2+ absorption owing to the high luminal Mg2+ concentration and lumen positive transepithelial voltage of +5mV[17]. The low expression of claudins in ileum and distal colon makes them highly permeable to ions.

TRPM6 and TRPM7 are expressed in the luminal side of enterocytes which help in transcellular pathway. The former is ubiquitously expressed whereas the latter is expressed majority in distal small intestine and colon in case of murine tissues.

FACTORS IN REGULATION:

Disturbed magnesium absorption by low magnesium diet in take which is partly attributed by changes in colon containing TRMP6 expression and paracellular rate of transport owing to electrochemical gradient. It is shown that , 25 dihydroxy vitaminD3 stimulates intestinal

Mg absorption exemplified by low vitD3 levels in patients of chronic renal disease having low Mg levels.VitD3 regulates the expression of claudins 2 and 12 involved in paracellular pathway and doesn't regulate the TRMP6 expression in kidneys.

Low and high Mg2+ intake affects calcium metabolism as shown in mice.[13-15] Though the actual mechanism is unknown, it is suggested that common transport mechanism from intestinal tract for both Ca and Mg suggested calcium sensing receptor CaSR has a regulatory role in this interaction.

TABLE 1 REGULATORY FACTORS IN MAGNESIUM ABSORPTION

Increased Mg reabsorption due to	**Decreased Mg reabsorption due to**
Parathyroid hormone,GH	Diuretics, fatty acids, phytates
Vitamin D, neomycin,	Phosphorus depletion,phosphates
Hypocalcemia, high protein intake	Hypercalcemia, low protein intake
Metabolic alkalosis	Metabolic acidosis
Intravascular volume depletion	Intravascular volume expansion
Hypomagnesemia and normal mucosal state	Hypermagnesemia and damaged mucosa
Increased requirement	Decreased requirement

MAGNESIUM STORAGE

Magnesium stored in bone as largest amount hence it act as aenerger of bone .There occurs continuous interchange of Mg within bone and blood. Low plasma Mg leads to activation of osteoclasts causing bone resorption[13,14]. Muscle fibres also store magnesium where it regulates contraction of muscle by opposing action of calcium.

DISTRIBUTION OF MAGNESIUM IN THE BODY:

- whole blood 2 to 4mg/100ml
- CSF 3mg/100ml(Mg in CSF ½ as high as in plasma)
- Muscle 21mg/100gm
- 70 percent of the total magnesium is combined with calcium and phosphorus in the complex salts of bone.
- Remainder in the soft tissues (liver and muscle -20mEq/l) and body fluids.It is the principal cation of the soft tissue.
- Hyperthyroidism increases the exchangeable mg, whereas it is reverse in hypothyroidism.
- Extracellular Mg contributes to only 1% of total Mg content which is found in serum and RBC.
- Serum Mg is available in three fractions; either ionized 60%, protein bound 30% or complexed with other anions 10%.
- RBC 5mEq/l. unbound portion of serum magnesium is the biologically active fraction.
- ICF 5 to 20 mmol/L of which majority remain combined to proteins, molecules having negative charge, ATP. Only 1-5% remain ionized form.

The skeletal 2% and ECF magnesium pools interchange freely with each other, but not interchange with the intracellular pool, muscle contains 20% exchangeable magnesium. Mostly50–60% of magnesium present as surface replacer of the hydroxyapatite[16], it is mineral component of bone.

Bone acts as reservoir pool of magnesium to buffer acute changes of plasma Mg levels. With age, the Mg levels of bone decrease thus making it unavailable during Mg deprivation.

RENAL HANDLING OF MAGNESIUM:

Kidney plays a role in maintaining plasma magnesium level within normal limits. About 98% of magnesium filtered at glomeruli is reabsorbed

- 2/3 rd of excreted magnesium excreted in the feces
- 0.75 mEq of Mg is lost daily in perspiration in normal health with normal diet. Loss is much increased with visible frank sweating
- 1/3rd into the urine; it varies with plasma magnesium concentration.

PROXIMAL TUBULE

Of the total serum magnesium, about 80% is filtered in kidneys, of which more than 95% is reabsorbed in tubular system.10-25% reabsorption takes place in PCT in adult kidney.

Compared to other ions, absorption of Mg in proximal tubules remain miniscule. As more and more water gets reabsorbed, Mg concentration increases and once gradient is generated passive paracellular transport takes place which leading to 10-25% of Mg reabsorption.[18-20]

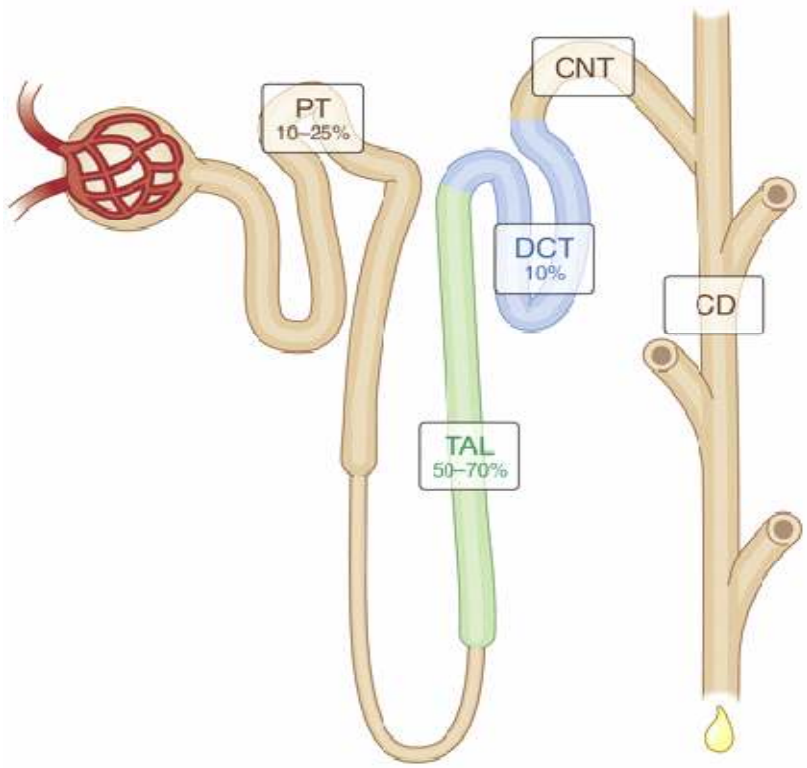


Fig 2 Magnesium reabsorption along the nephron

LOOP OF HENLE -THICK ASCENDING LIMB

Majority of magnesium reabsorption occurs via cortical dense ascending limb (CTAL) of Loop of Henle (2/3 rd of magnesium).This is a passive paracellular transport driven by NKCC2 created lumen positive trans epithelial voltage. Paracellin-1 regulates paracellular through creation of pore permitting calcium and magnesium flow down their electrochemical gradient. It is shown that claudins 16 and 19 play role by forming cation selective tight junctions.

Na^+ and Cl^- enter the ascending loop cells through $Na^+K^+Cl^{2-}$ channel and leaves the cells through Na^+K^+ ATP ase, kidney specific Cl^- channels.K^+ gets recycled into lumen via renal outer medullary K^+ channel. This maintains the positive potential in lumen which activates Mg transport.Use of diuretics like frusemide which inhibit NKCC2 channel abolishes this positive potential leading to increased excretion of Mg causing hypomagnesemia.

Magnesium reabsorption in cortical thick ascending is influenced by many hormones (such as PTH, Calcitonin, Glucagon, Arginine, Vasopressin) as well as no hormonal factors (magnesium restriction, acid base balance, potassium depletion)[22-23].

Restriction of dietary magnesium leads to renal magnesium conservation along with diminished urinary excretion of magnesium and this adaptation of magnesium transport occurs both in CTAL and distal tubule.

Magnesium and calcium reabsorption is inhibited by elevation of magnesium and calcium concentration, leading to hypercalciuria and hypermagnesuria.

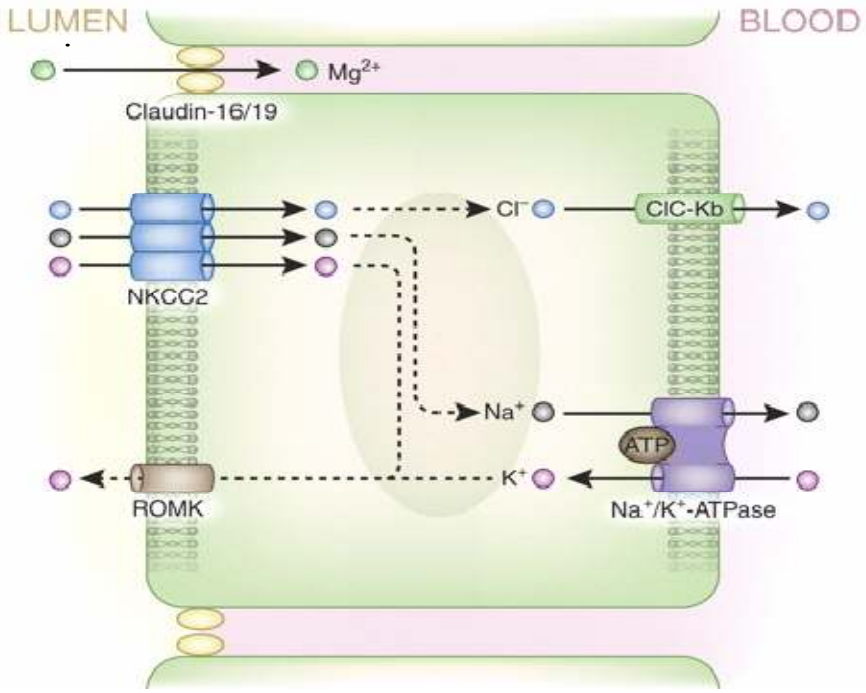
This phenomenon is explained by the identification of a Ca-Mg sensing receptor located on the peritubular sides of TAL and distal tubule cells. Salt absorption in CTAL is diminished by loop diuretics such as furosemide, bumetanide, other factors decreasing magnesium reabsorption are potassium depletion, phosphate restriction, etc,[21]

Ca-Mg sensing receptors:

Ca-Mg sensing receptor localized to the basolateral membrane influences the calcium-magnesium transport in TAL. It is activated by a rise in plasma Ca-Mg receptor causing reduction in NaCl reabsorption and Vte, thus inhibiting reabsorption of Calcium and Magnesium.

The signal transduction pathway includes stimulation of arachidonic acid (AA) production through direct or indirect activation of phospholipase A2 (PLA2), which is metabolized via the cytochrome P450 pathway to active metabolite that inhibits the apical potassium channel and, perhaps, the Na^+, K^+,$2Cl^-$ co transporter activity, thereby reducing the lumen-positive voltage and paracellular transport of divalent cations. The calcium-magnesium-sensing receptor probably also directly or indirectly (by raising intracellular Ca2+) inhibits adenylate cyclase and causes decrease of hormone stimulated divalent cation transport.

Fig 3 MAGNESIUM TRANSPORT PATHWAY IN THE LOOP OF HENLE



DISTAL CONVOLUTED TUBULE

10% of magnesium reabsorption takes place in DCT, which is the most important part in fine adjustment of renal magnesium excretion. Magnesium cation abnormal, which is coded by TRPM6 gene facilitates apical entry of magnesium, while basolateral exit is through a Mg/Na interchange mechanism.

Active transcellular transport mechanism is the main mechanism for Mg reabsorption in DCT, and is closely related to NCCT generated lumen positive voltage[25]. Mutation in NCCT leads to hypokalemia, hypocalciuria and hypermagnesuria. Hypomagnesemia is linked with hypokalemia frequently, because reduced Mg in ICF which release the Mg dependant inhibition ROMK channels leading to enhanced K^+ loss in urine.

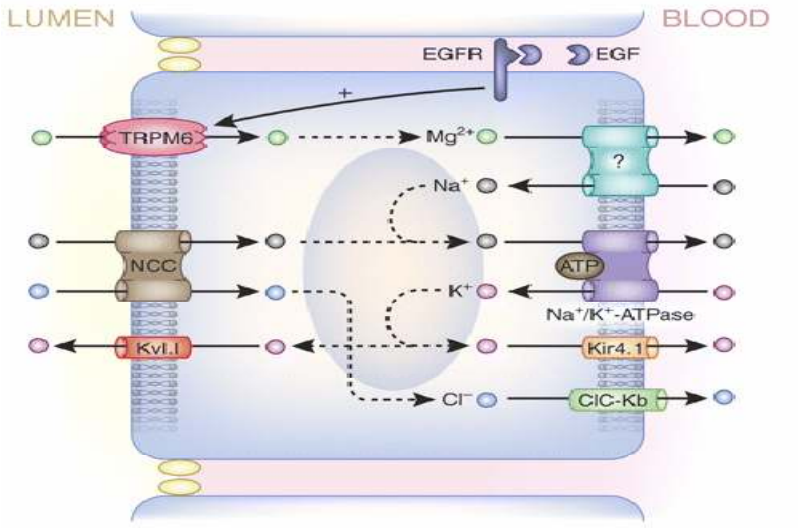


FIG 4 Mg transport pathway in DCT.

TRMP Mg channel is regulated by EGF. The transmembrane potential is maintained by kv1.1k+ channels. Na+K+ ATPase at the basolateral membrane is balanced by transcription factor HNF1B. kir4.1 which is responsible for K+ recycling at basolateral side of cells.

REGULATORY FACTORS

Pro endothelial growth factor is expressed only in distal convoluted tubule which on cleavage gets activated to EGF which in turn regulates TRMP 6 activity. Oestrogen stimulates TRMP 6 activity. Hypermagnesuria in post menopausal women can be reversed by oestrogen substitution therapy.

PTH diminishes excretion. Increased Ca and thyroid hormones, ADH, Growth hormone, aldosterone, alcohol, Ammonium chloride all increases excretion. Final magnesium concentration determined by interchange within passive mechanism and adjustment through active transporters present in absorption pathway after filtration.

ASSESSMENT OF MAGNESIUM

Assessment of Serum magnesium concentration is the routinely done test. But correlation between serum Mg and total body Mg is not well because as only 0.3% of it is in the serum.

Magnesium is in:

1. Serum
2. RBC
3. Leukocyte
4. Muscle

Measured by: Balance studies, urine spot magnesium, ion uptake assay and magnesium retention test.

Measurement of free Mg levels by: Fluorescent probes and ion selective electrodes, NMR spectroscopy, Metallochrome dyes.[27]

In certain individuals, there may be a reduced total body magnesium, even though their serum Mg concentration are within limit and this condition is known as subtle chronic magnesium deficiency. Also there are some individuals whose total body magnesium content is within the physiological limits but serum Mg levels are low. Higher serum Mg levels are seen in vegetarians, after short periods of minimal exercise. During third trimester of pregnancy and after endurance exercises, lower serum Mg levels are observed. Hemolysis and serum bilirubin levels have a significant influence over the levels of Mg. Intra-individual variability is also seen.

Mg concentration is closely maintained within normal limits in healthy individuals. The reference range of total magnesium levels in adult blood serum varies between 0.65-1.05 mmol/L ,ionized magnesium level range is between 0.55-0.75 mmol/L. Mg levels in serum is lower than that of in RBCs. Hence to avoid misinterpretation of Mg levels, one should be aware enough to avoid hemolysis.

In spite of many limitations, serum Mg levels remains as standard for a patient's Mg status evaluation. Serum Mg measurement is feasible and not too expensive. It also helps in detecting rapid extracellular Mg level changes.

URINARY MAGNESIUM LEVELS:

Measurement of Magnesium levels excreted in urine helps to know about the etiology for hypomagnesemia. Renal wasting of Mg is associated with higher urinary excretion whereas inadequate intake or absorption is associated with lower Mg levels in the urine. Since the urinary excretion level of Mg varies with circardian rhythm, one should always collect a 24hr urine specimen for appropriate evaluation. Fractional Mg excretion on a urinary spot specimen is calculated using the formula as follows.

$$FEMg = UMg \times PMg \times 100/0.7 \times PMg \times UCr$$

Where FE Mg - Fractional Mg excretion

U Mg - Urinary Mg levels

P Mg - plasma Mg levels

UCr - urinary creatinine concentration.

MAGNESIUM LOADING TEST:

To detect normo magnesemic magnesium depletion in critical care patients, Mg loading test is used[26].When compared with serum test, it is the most sensitive test to detect the low Mg and assess the exchangeable Mg.

MAGNESIUM LVELS ASSESSMENT BY ION UPTAKE ASSAY

Magnesium available in the forms of ^{24}Mg, ^{25}Mg,^{26}Mg.^{26}Mg is used for assessment of intestinal Mg absorption.[28]^{28}Mg is radioactive for scientific use .In this method we can assess the initial change of ion content in the cells

FUNCTION OF MAGNESIUM

1. Cofactor in more than 300 enzymatic reaction; also involved in hormone binding protein, energy production and ATP which is required for muscle fibre contraction, protein and fat synthesis, cell reproduction and transport of substances across the cell barrier, glucose utilization, methyl group transfer.
2. Plays major role in neuronal activity and muscle action, neurotransmitter release[29]
3. Cardiac function, regulate heart beat, vascular tone, platelet activated thrombosis[28]
4. Endocrine function and bone formation.
5. Crucial to glucose and fat break down, ATP metabolism, also for protein and antioxidants synthesis
6. Also regulates cholesterol production

7. Maintains DNA structure and RNA, repair of DNA damage
8. Maintains mineral balance
9. Anticonvulsant
10. Supports a healthy immune system, and bone strength
11. For protein synthesis and blood glucose regulation.

USES:

- Laxative for constipation
- Bowel preparation for surgical or diagnostic procedures.
- Antacid for acid indigestion.
- To treat hypertension, dyslipidemia, mitral valve prolapsed, irregular heartbeat, chest pain , myocardial infarction
- Used to treat attention deficit-hyperactivity disorder and anxiety
- also for Lyme disease and fibromyalgia ,restless leg syndrome
- to reduce blood glucose in diabetes and chronic fatigue syndrome
- for kidney stones and migraine, osteoporosis
- for premenstrual syndrome , leg cramps and altitude sickness
- also used to treat asthma and hay fever
- multiple sclerosis, to preventing hearing loss
- To increase energy and endurance and for urinary incontinence

- Magnesium may be used tropically to treat skin ulcers, carbuncles, boils
- Magnesium used as cold and hot compressor to treating severe skin infections
- Magnesium is useful for bone growth

MAGNESIUM DEFICIENCY CAUSED BY

Development of hypomagnesemia in critically ill patients categorized into decreased intake of Mg containing diet, those having disturbed intracellular-extracellular distribution and those with increased intestinal loss and renal loss[30-32]

Decreased intake is a important determinant of magnesium levels .decreased intake of green leafy vegetables (chlorophyll Mg chelate of porphyrin).

Serum magnesium level may fall in a number of clinical settings and contributes to a guarded prognosis for the patient especially when below 1.7mg/dl.

Acutely ill patients who develop hypomagnesemia fall into:

- Those having low intake of Mg
- Those having disturbed intracellular and extracellular distribution
- Kidney or gastrointestinal tract loss

HYPOMAGNESEMIA CAUSES:

I. Impaired intestinal absorption

    1. Primary infantile hypomagnesemia
    2. Malabsorption syndromes
    3. Vitamin D deficiency

II. Increased intestinal loss

    1. Protracted vomiting and diarrhea
    2. Intestinal drainage and fistulae

III. Impaired renal tubular reabsorption

    1. Genetic magnesium-wasting syndromes
        A. Gitelman syndrome
        B. Bartter syndrome
        C. Paracellin-1 mutations
        D. Na^+ K^+ATPase g-subunit mutations (FXYD2)
        E. Autosomal dominant, with low bone mass
    2. Acquired renal disease
        A. Tubulo interstitial disease
        B. Post obstruction, ATN (diuretic phase)
        C. Renal transplantation

3. Drugs and toxin

    A. Diuretics (loop, thiazide, osmotic)

    B. Cisplatin

    C. Pentamidine, foscarnet

    D. Cyclosporine

    E. Aminoglycosides, amphotericin B

IV. Extracellular fluid volume expansion

1. SIADH
2. Diabetes mellitus
3. Hyper calcemia
4. Hyper aldosteronism
5. Metabolic acidosis
6. Phosphate depletion
7. Hyperthyroidism

V. Rapid shifts from extracellular fluid

1. Rapid intracellular redistribution

    A. Recovery from diabetic ketoacidosis

    B. Refeeding syndrome and catecholamines

    C. Correction of respiratory acidosis

2) Accelerated bone formation

A. Treatment of vitamin D deficiency

B. Post parathyroidectomy

C. Osteoblastic metastasis

3) Others:

A. Malnutrition

B. Phosphorous deficiency

C. Total parenteral nutrition

D. Citrated blood products

E. Alcohol abuse

F. Hungry bone syndrome

G. Cardiopulmonary bypass

H. Hypoalbuminemia

I. Pancreatitis, burns, excessive sweating

J. Pregnancy (3rd trimester) and lactation

CLINICAL AND LABORATORY FINDINGS

Alterations in neuromuscular function

Ataxia, tetany, seizures, tremor, nystagmus, apathy, vertigo, irritabilty, depression, psychosis, delirium, Muscle fasciculation, muscular weakness, alteration in mental status.

Cardiovascular symptoms

Arrythmia like atrial fibrillation, ventricular tachycardia, supraventricular tachycardia, torsades de pointes, Hypertension, Vasospasm, Increased vascular resistance

Electrocardiogram changes:

QT interval prolongation and PR interval prolongation

Widened QRS complex

Flattening or inversion of T wave

Depression of ST segment

Endocrine:

Stimulates secretion of parathyroid hormone (PTH) in mild cases, Suppresses PTH secretion in severe cases, Insulin resistance

Electrolyte disturbances

Decreased potassium, calcium and phosphorous

Respiratory system

Bronchoconstriction, Muscle weakness and Respiratory failure

Miscellaneous

Ileus, Increase in the levels of proinflammatory cytokines, Potentiation, of nephrotoxicity of cyclosporine and ototoxicity of gentamicin.

MAGNESIUM IN DISEASES

SEPSIS:

Magnesium plays a significant role in patients with sepsis. Hypomagnesemia is linked with increased release of proinflammatory cytokines and endothelin[32]. Progressive deficiency of hypomagnesemia are strongly associated with increased mortality reported by SALEM et al showed in his study that hypomagnesemia was associated with increased mortality in patients with sepsis and repletion of magnesium protects against Endotoxin mediated damage.

HARKEMA et al did a study and he infused ATP-MgCl2 to the animal models having sepsis and shock .It was found to refine the organ function and prolong the survival time. This was due to the down regulation of inflammatory cytokines release like TNF-alpha and IL-6. SOLIMAN ET AL showed in his study that sepsis is an independent risk factor for developing hypomagnesaemia in ICU set up.

CARDIAC ARRHYTHMIAS

Mg has proven to be playing a good role in pathogenesis and treatment of supraventricular arrhythmias. Mg supplementation has increased the chance of conversion of atrial fibrillation to sinus rhythm. Magnesium was found to be superior to amiadarone in conversion of acute atrial tachyarrhythmia's according to MORAN and co studies[33].It was postulated that Mg exerts its anti arrhythmic action by blocking slow calcium channels and inhibiting sodium potassium ATP ase function.

ACUTE MYOCARDIAL INFARCTION

Magnesium blocks calcium flux into ischemic myocardial cells. It reduces vascular tone[34-36]. It reduces peripheral resistance. Magnesium increases the threshold for depolarisation. Thus helps to overcome the arrhythmias associated with acute myocardial infarction.

CARDIAC FAILURE AND MALIGNANT ARRHYTHMIAS

Left ventricular failure and biventricular failure are associated hypomagnesemia. Elevated magnesuria is seen in these patients and it is controlled by loop diuretics. Animal studies have suggested that it would be beneficial to include magnesium in the acute management protocol of malignant arrhythmias with significant dysfunction of ventricles.

BASHIR *et al* conducted a randomized, double blind crossover trial in which he tried using long term oral magnesium administration in congestive heart failure. The study was successful in showing a decrease in non-sustained monomorphic ventricular tachycardia (mVT) in nearly one fourth of patients. 21 patients are included in the study. Similar results are obtained by SUETA *et al* in cases with symptomatic heart failure which was symptomatic treated with magnesium or placebo. Of the 30 patients included, none had a previous history of symptomatic arrhythmias.

CEREMUZYNSKI *et al* showed excessive urinary magnesium in 72% and hypomagnesaemia in 38% of 78 patients with congestive heart failure with less than 40 % EF on admission. This study showed that administration of magnesium

decreased the incidences of non-sustained mVT largely but showed no difference in the adverse events risk.

1068 patients were included in the PROMISE STUDY with New York Class III/IV heart failure for a RCT of milrinone. Magnesium levels were tested for all individuals during the trial. Serum magnesium was not a separate risk factor for sudden death.

There is only some data to support that there is use of magnesium in patients with ventricular dysfunction who are presenting with a malignant arrhythmia. Until the other studies are over it should be kept reserved for those individuals with proven hypomagnesaemia.

ATRIAL FIBRILLATION

Sinus node function is not affected by magnesium. It delays atrioventricular nodal conduction and atrial refractory period.[37-38] A trial on cardioversion of acute atrial fibrillation (AF) has shown improvement but this involved the patients with AVN tachycardia and compared the use of magnesium with verapamil. The other study showed there was some improvement in ventricular rate control but this was

not better than digoxin. This was contradicted by Frick *et al* who showed there was no effect on heart rate or variability in rate in individuals with chronic AF.

Magnesium was proved to act as an antagonist of digoxin indirectly at the sarcolemmal $Na^{+}K^{+}$ATP ase pump. It has shown improvement in lowering the episodes of ventricular arrhythmias which is associated with digoxin toxicity. However the gold standard test remains Fab antibodies.

TORSADE DE POINTES

Torsade de pointes (TdP) is a form of polymorphic ventricular arrhythmia. It is associated with prolongation of QT interval. It is associated with the prominent U waves on the resting electrocardiogram. There is prolonged repolarisation and the development of early after depolarization on ECG. It may progress to ventricular fibrillation. In the long QT syndromes potassium ion channel dysfunction causes an intracellular surplus of positive charge, so delay repolarisation is mainly because of efflux of potassium ions. Delay of inactivation of calcium ion channels causes in late inflow causing EADs.

These may reach threshold amplitude causing a ventricular arrhythmia. As the deep sub endocardium is most vulnerable to prolonged repolarisation and the

development of EAD the heterogeneous state of the myocardium causes a specific type of re-entrant arrhythmia. This is seen in the TdP pattern on ECG.

The long QT syndrome which has the risk of development of TdP may be congenital or iatrogenic. It is associated with:

- Anti arrhythmics class Ia and II
- Butyrophenones and phenothiazines
- Non-sedative antihistamines
- Tricyclic antidepressant and cocaine
- Antibiotics especially macrolides
- Organophosphates
- Antifungals

It is also seen in subarachnoid haemorrhage, starvation and bradycardias. The aim of treatment in TdP are (a) to decrease the QT interval and (b) to alter the after depolarization effect. Present management of TdP is based on theoretical a concept which is supported by experimental evidence as there are no randomized control trials.

Intravenous magnesium sulphate 2g over one to two minutes reduces EADs in the emergency situation. Studies support the fact that it reduces the amplitude of EADs to sub-threshold levels, It does so by inhibiting the influx of calcium. This has to be accompanied by correction of hypokalemia to a serum concentration of >4.5 mmol/l. Lignocaine decreases the duration of action potential. Thus it indirectly decreases the production of triggered potentials. However, this effect is inconsistent with a reported success rate of only 50%.

There is an inverse relation between the heart rate and the repolarisation duration. So magnesium with or without potassium should be associated with increase in the heart rate. Magnesium is relatively safe. It is simple intervention in TdP. It is the first line drug therapy in TdP.

MAGNESIUM AND HYPERTENSION

Magnesium has a vasodilatory effect, patho-physiological role in systemic hypertension[39-41]. According to various studies done there was an inverse relationship between blood pressure and magnesium. Hypomagnesemia has been associated with left ventricular hypertrophy and high blood pressure. Some of the investigators have shown that patients with hypomagnesemia may need higher doses of anti hypertensive drugs for treatment.

However, there was a considerable research done and the exact underlying cause of this remain unclear for decreased magnesium levels in patients with hypertension. It can be taken in a way that low magnesium in diet or disturbance in metabolism of magnesium can cause vasospasm and endothelial damage .Combined effect of hypomagnesemia with stress and catecholamine secretion which enhances the entry of calcium into vascular smooth muscle cells which again leads to coronary spasm and increased arteriolar tone.

Increased blood pressure, its complication may be due to smooth muscle contraction and enhanced calcium influx into the cell.

Magnesium is also known as natural calcium antagonist and magnesium acts on calcium channel present in vascular smooth muscle which leads to lowers the arterial blood pressure properties. Which again results to reduce the peripheral and also cerebral vascular resistance. Competitive inhibition of calcium binding and its influx exerts vasodilatation. In various animal studies has been proved that vasodilatation properties of magnesium, these studies are tells that we can reduce the blood pressure and vascular tone modification by the way of minor change in magnesium concentrations.

MAGNESIUM AND DM

Hypomagnesemia in DM caused by

1. Intake of diet was reduced in case of diabetics due to diabetic gastroparesis, esophageal dysfunction.
2. Autonomic dysfunction which leads to diarrhea causing excessive magnesium loss.
3. Increased renal magnesium loss which due to excessive filtered load and filtration osmotic diuresis due to glucosuria ,increased volume replacement also due to diabetic ketoacidosis, microalbuminuria, overt proteinuria and by hypoalbuminemia,

4. Reduced renal reabsorption because of phosphate , potassium depletion insulin deficiency, diabetic ketoacidosis,

HYPOMAGNESEMIA AND ITS OUTCOMES IN TYPE 2 DM

There is considerable evidence to suggest that hypomagnesemia may adversely affect various aspects of cellular physiology. Available data suggest that low Mg levels may enhance endothelial cell dysfunction and thrombogenesis by the way of enhanced platelet aggregation and vascular calcifications.

Hypomagnesemia may also induce proinflammatory and profibrogenic response, augment the vasoconstriction and hypertension and stimulation of aldosterone, reduce the protective enzymes against oxidative stress. Hence magnesium plays a role in DNA synthesis and repair and its deficiency may interrupt the regulation of apoptosis and normal cell growth

CADIOVASCULAR:

Resnick et al showed in a study magnesium concentration was low in both hypertension and diabetic individuals[42].Risk in Communities (ARIC) Study, a multicenter, prospective cohort study was done among men with diabetes showed that there was an inverse association between risk for coronary heart disease and serum magnesium.

DIABETIC RETINOPATHY:

Two cross-sectional studies shown that hypomagnesemia has a link with diabetic retinopathy.[43-44]

NEPHROPATHY

Corsonello et al was found that serum ionized Mg was low in micro albuminuric and overt proteinuria in patients with diabetes compared with non micro albuminuric group. Also hypomagnesemia associated with faster rate of renal function deterioration according to reports in recent retrospective study.

There are study which shows hypomagnesemia is related to dyslipidemia and neurologic abnormalities. Lots of efforts are needed to minimize hypomagnesemia in diabetic patients because which is linked with micro and macrovascular complications

INSULIN DEFICIENCY AND / RESISTANCE

Due to anti magnesiuric effects of insulin in both the TAL and the DCT, renal magnesium wasting may be exacerbated by insulin defeciency or resistance [46]

Possible underlying mechanisms

The mechanism of worsening of existing diabetes in patients having hypomagnesemia is not clear. It has been suggested that magnesium regulates cellular glucose metabolism, it plays a significant role as a cofactor for various enzymes and which also acts as a second messenger for insulin.

It was also discovered that insulin increases intracellular magnesium uptake and thereby mediates diverse effects of insulin. Hypomagnesemia may cause disturbed cellular glucose transport, decreased pancreatic insulin release, defective post-receptor insulin signalling and changes in insulin– receptor interactions and thereby increase insulin resistance.

Therapeutic considerations

Two studies studied the effect of magnesium supplementation in non-diabetic insulin-resistant individuals:

One study in 60 non-diabetic hypomagnesemic individuals shows in a double-blind, randomized trial over 3 months, that daily supplementation of 300 mg (12.3mmol) magnesium greatly enhanced insulin sensitivity. This information was proved in a recent placebo-controlled randomized trial in 52 normo magnesemic, but overweight and insulin-resistant individuals, in whom Mg administration

Over 6 months led to a great improvement of fasting plasma glucose and insulin sensitivity indices as against the placebo. Whether known T2DM patients benefit from the supplementation of magnesium was studied in a meta-analysis of nine randomized-controlled trials enrolling 370 participants. Dosage, indications and inclusion criteria differed.

Number of individuals in the single studies were relatively less and the outcome variable. Oral magnesium administration at a dose of 15mmol/day used as supplement therapy for 4–16 weeks resulted in of lowering fasting glucose levels, but only slightly lowered HbA1C and increasing HDL-C[45]. One study, studying the effect on lipid profiles that was not studied in the above meta analysis, as a combination of magnesium and vitamin C and E was used, resulted in an increase in HDL-C and Apo A1 but no other variations in lipids including triglycerides.

Magnesium supplements singly or in combination with other supplements (i.e. Zinc, vitamin E, C and B complex) have also been shown to be useful in cases of diabetic neuropathy and depression.

IN DIURETIC USAGE

Magnesiuria may be caused by two types of diuretics; this effect was lower in thiazides compared to loop diuretics. Which may be due to the site of action of diuretics, thiazides acts in DCT which have lower amount of intraluminal Mg also inhibit NaCl co-transporter which induce the hyperpolarization of the DCT plasma membrane and there is a more favorable transmembrane electrical gradient for Mg reabsorption, in spite of that chronic thiazide usage inhibits TRMP6 channels leading to hypomagnesemia.

It also mimics Gitelman's syndrome as it also inhibits $Na^{+}Cl^{-}$ cotransporter leading to sodium excretion. With help of this observation a experiment was done in mice by giving chronic thiazide therapy which showed reduced TRPM6 expression and increased magnesiuria

MAGNESIUM IN DIABETIC KETOACIDOSIS

Major magnesium loss was noted in case of diabetic ketoacidosis in early treatment stage. This loss is due to insulin therapy and fluid therapy, phosphate replacement .In patients with diabetic ketoacidosis phosphate replacement therapy.

BUTLER and ASSOCIATES have suggest the inclusion of magnesium replacement in the management of diabetic ketoacidosis. However, the AMERICAN DIABETIC ASSOCIATION recommendation is to supplement magnesium only in patients with documented hypomagnesemia.[42]

MAGNESIUM IN METABOLIC ACIDOSIS:

Metabolic acidosis plays a role in enhancing serum ionized Mg concentration as well as ultrafiltrable Mg load for renal excretion and increase protonation of the Mg channel in the DCT also inhibit the Mg entry into cell, so that hypomagnesemia can occurs.

NIJENHUIS et al found that reduced expression of TRPM6 in case of induced chronic metabolic acidosis in mice.

MAGNESIUM AND METABOLIC SYNDROME:

The triad of hypertension, obesity and impaired glucose tolerance constitute metabolic syndrome. Magnesium deficiency increases insulin resistance in patients with metabolic syndrome as well as type 2 DM[47,48]. Hypomagnesemia alters glucose entry into the cells. This results in impaired activity of tyrosine kinase and modification of intracellular signaling and processing. There was a prospective study which showed that there is inverse relationship between intake of magnesium and incidence of metabolic syndrome.

MAGNESIUM AND ALCOHOL

Hypomagnesemia is a common phenomenon in chronic alcoholics. Rising alcohol levels in the blood causes increased urinary excretion of magnesium acutely[49]. DUNN and WALSER showed in their study that if the alcoholic patients are taking low magnesium diet, urinary magnesium excretion was not high. Malnutrition may be the cause for depletion of magnesium in alcoholics . Hypophophatemia is found to be associated with hypomagnesemia in alcoholics. There is a possibility that depletion of magnesium is secondary to decrease in phosphate levels.

ALCOHOL WITHDRAWAL

As already stated that alcoholism leads to hypomagnesemia by increased loss of magnesium in urine, malnutrition, gastrointestinal magnesium loss, deficiency of phosphate and deficiency of vitamin D. There are animal studies to support the role of magnesium therapy in alcohol withdrawal. There is only one randomized control trial, in humans where magnesium supplementation in alcohol withdrawal was studied. But it failed to demonstrate significant benefit.

The American Society of Addiction Medicine on the pharmacological management of alcohol withdrawal practice guidelines says there is no data that severity of withdrawal or incidence of delirium or occurrence of seizures were reduced by magnesium supplementation.

ACUTE CEREBRAL ISCHEMIA

Magnesium enhances cerebral blood flow, in animal studies shows that association of reduced levels of extracellular magnesium and cerebral vasospasm[50-53].Mg buffers intracellular calcium and counteracts calcium actions in voltage gated channels leading to blocking of NMDA receptor and regeneration of ATP.

Many epidemiologic studies was done among those people consuming magnesium rich diet which showed a decrease in stroke rates and death from stroke which initiates the interest in the use of magnesium which was followed by number of animal studies was done. This study showed that experimentally induced cerebral infarctions size reduced by magnesium supplementation.

A study was done in rats with middle cerebral artery occlusion by LEE and coworkers. It showed that there was decreased demand for energy and prevention of energy depletion occurs when administration of magnesium and mexilitine, a sodium channel blocker separately.[51]

Schmid-Elsaesser and colleagues induced cerebral ischemia in rats. They found that administration of magnesium and the antioxidant-tirilazad decreased the infarct volume by 25% when given separately[53].In combination, these agents decrease the infarct volume by 59%. They also found that with hypothermia these agents were able to completely abolish the cortical infarcts.

It is found in studies that there is a significant correlation between low cerebrospinal fluid Magnesium concentrations and size of the infarct and intensity of residual neurologic deficit.

MIGRAINE

Magnesium does have role in migraine treatment as evidenced by the following reasons.

1. Serotonin receptors found to be altered ionized magnesium.
2. Improvement in cerebral vasospasm is seen by a greater ratio of ionized calcium and ionized magnesium.

There are studies which say magnesium can help in prophylaxis. There are two studies to suggest that magnesium has a role in the management of acute attack of migraine. MAUSKOP *et al* was successful in showing that there was relief of headache within 15 minutes of administration of intravenous magnesium in 32 of 40 patients studied who had migraine, cluster headache, or tension headache.

In 18 this lasted for one day and low levels of serum magnesium was found in 16 of them. DEMIRKAYA *et al* showed there was reduction of headache in 13 of 15 patients with migraine after administration of intravenous magnesium.

PREECLAMPSIA AND ECLAMPSIA

The neuromuscular transmission is found to be altered by magnesium. Magnesium competes with calcium entry into the presynaptic endings.[54] It reduces the effect of acetylcholine on post synaptic receptors on muscles. Magnesium also raises the threshold for axonal excitation. Thus it has depressant effect on the synapses in the nervous system. Magnesium has been found to potentiate the action of non depolarizing neuromuscular blockers.

Preeclampsia complicates 7% of the pregnancies. When patients with preeclampsia develop seizures, the condition is termed as eclampsia. Several mechanisms are involved in prevention of seizure activity by magnesium. These include increase in cerebral flow, stabilization of neuronal membrane, prevention of vasospasm in cerebrum and anti platelet action[54-57] .In prichards regimen, magnesium sulphate is given as 4g iv stat followed by 2-3g/hr infusion to maintain a serum concentration of 5-7 mg/dl. Mg toxicity has to be monitored. This toxicity is manifested by the loss of deep tendon reflexes, muscular weakness leading to respiratory failure, complete heart block and cardiac arrest.

ASTHMA

Okayama and colleague study has shown remarkable improvement in FEV1 of asthmatics during acute exacerbation by administration of magnesium[58-60]. Rapid administration of Mg as infusion has decreased need for intubation due to reversal of bronchospasm.

Inhaled Mg has decreased bronchoconstrictor effect of metabisulfides leading to bronchodilatation. The evidence that Mg is a bronchodilator is convincing and adequate to put forth its use as a drug in refractory asthma.

Magnesium causes changes in extracellular calcium influx leading to changes in intracellular phosphorylation reactions. It interferes with mast cell degranulation and suppresses the neutrophilic burst which causes inflammatory bronchoconstriction. The mast cell degranulation is stimulated by increasing ICF calcium levels which is counteracted by magnesium.

The bronchodilatory effect of salbutamol is improved by use of Mg. Magnesium decreases histamine induced bronchospasm thereby relieving the symptoms.

SKOBELOFF *et al* showed that administration of magnesium in cases with severe exacerbation of bronchial asthma in emergency room showed remarkable

improvement in peak expiratory flow rate thereby increasing the number of discharge from emergency room. Similar results were obtained from Cochrane systemic review conducted in 1999which substantiated use of magnesium sulphate in acute severe asthma.

Use of magnesium as a single drug in nebulization is still experimental but isotonic magnesium with beta agonist has shown fruitful results. MOLLOY et al in a study that magnesium supplementation showed significant effect in respiratory muscle weakness in cases who had hypomagnesemia.

MAGNESIUM AND SNAKE BITE

Snake venom contains toxic and nontoxic substances which damage the renal tubules. 75% of magnesium reabsorbed into renal tubules, 3-5% excreted in urine, hence renal tubular damage may increases the renal Mg loss leads to magnesium deficiency.

Hypoxia or anoxia caused by snake venom increases the intracellular Mg concentration due to shift of extracellular Mg into intracellular fluid also induces magnesium deficiency.

EFFECTS OF MAGNESIUM IN CALCIUM METABOLISM

Calcium metabolism has been found to altered by magnesium depletion in various studies done in humans and animals.[63] The lower levels of calcium changes internal mechanisms which controls calcium levels leaving external calcium balance unchanged. Parathyroid hormone secretion is stimulated by low magnesium and low calcium levels. Changes in either of these cations has significant effect on PTH secretion. Thereby simultaneous increase in one cation with decreased levels of other cation leaves the PTH levels unchanged .In in vitro studies the combined concentration of calcium and magnesium and parathyroid release showed a first order relationship.

In acute magnesium depletion magnesium has a direct effect on PTH, whereas in chronic Mg depletion parathyroid function appears to affected in opposite direction. In ANAST and colleagues, MENNES and associates studies showed that intravenous administration of magnesium in hypomagnesemic patients has increased the PTH levels. Hypomagnesemia induced hypocalcemia also result from skeletal resistance to PTH according to various studies. In vivo studies done in hypomagnesemic dogs and rats and monkeys found that normal calcemic response to PTH.

Studies in human performed by Estep and associates in hypomagnesemic alcoholic patients, MULDOWNEY and coworkers in magnesium depletion secondary to malabsorption syndrome and Woodard and colleagues in patients with diarrhoea showed an impaired calcemic response from PTH. CHASE and SLATOPOLSKY found a normal calcemic response from PTH in two hypocalcemic hypomagnesemic adults.

There are several factors that lead to low calcium levels due to depletion of magnesium. As well loss of Mg ion from the bone leads to deposition of calcium rendering the bone resistant to PTH action. In early course the secretion of PTH is decreased followed by resistant to PTH later. Thus both the levels of Mg and duration of hypomagnesemia lead to difference in response of bone to PTH.

EFFECTS OF MAGNESIUM DEPLETION ON POTASSIUM AND OTHER INTRACELLULAR SUBSTANCES

In various studies conducted, patients with hypokalemia are also hypomagnesemic[61-62]. Studies conducted on patients with alcohol and diabetic ketoacidosis reported coexistence of hypomagnesemia and hypokalemia more commonly.

Depletion of potassium were of two types,

1. Combined intracellular and extra cellular depletion.
2. Intracellular depletion alone .Potassium repletion is also accomplished with administration of magnesium.

Diuretic therapy often led to refractory potassium depletion which proved repletion of magnesium is necessary to normalize potassium. This was supported by studies conducted on animals in which myocardial depletion of potassium was prevented by infusion of magnesium. This is due to stimulatory effect on Na K ATP ase pump.

There is also direct effect of magnesium on sarcolemmal potassium channels due to compete with calcium ion. In other hand aldosterone is increased in kaliuresis due to magnesium depletion. The potassium rich diet

leads to more magnesium retention and in many conditions it is not possible to increase either of these ions without replenishing the other one there are reports in which supplementation with potassium induced tetany there are reports in which supplementation with potassium induced tetany as the serum calcium and magnesium values dropped due to rise in serum potassium.

This was reversed by supplementation with magnesium ions thereby explaining the fact decreased magnesium resulted in tetany due to coexistence of hypocalcemia occurring as a result of potassium supplementation. Furthermore, magnesium depletion led to depletion of muscle phosphorus as it caused rhabdomyolysis due to magnesium dependent phosphate depletion.

MAGNESIUM IN DIGITALIS TOXICITY:

In digitalis toxicity, digitalis acts on $Na^{+}K^{+}$ATP ase pump inhibiting its action leading to in the rhythm disturbances .The transmembrane potassium gradient produced in digitalis toxicity can be managed effectively by using magnesium which is cofactor in regulating ion transport system

In case of severe digitalis toxicity, Fab antibodies is the treatment of choice but Mg is a effective temporary measure in management of severe digitalis toxicity. Magnesium use has been proved to be safe, cost effective and easy to use.

METHODS AND MATERIALS

STUDY GROUP	:	Patients admitted in intensive medical care unit at KMCH who satisfied inclusion criteria
STUDY DESIGN	:	Cross-Sectional study
PLACE OF STUDY	:	Intensive medical care unit Kilpauk Medical College and Hospital, Chennai–10
DURATION OF STUDY	:	April 2014 to September 2014
CONFLICT OF INTEREST	:	Nil
SAMPLE SIZE	**:**	100
CONSENT	**:**	Patients taken into the study only after getting a written informed consent.

COLLABORATING DEPARTMENTS:

Department of General Medicine (Intensive medical care unit), and

Department of Biochemistry,

Kilpauk medical college and hospital, Chennai-10.

INCLUSION CRITERIA

These includes patients admitted in ICU with

- Cardiac Failure
- Respiratory Failure
- Poisoning
- Snake bite
- Sepsis
- Cerebro vascular accident
- Status epilepticus
- Diabetic Keto Acidosis

EXCLUSION CRITERIA:

- Patients who had previously documented Hypomagnesemia.
- Patients with Renal failure and those who have magnesium more than 2.5mg/dl.
- Patients who were on Magnesium supplementation and Blood Transfusion.

METHODOLOGY

- The data of each patient were collected in the specific proforma which included detailed history and thorough physical examination.
- Serum Magnesium estimated within 24 hours of admission.
- CBC, RFT, LFT, Urine routine, ECG, ECHO.
- CXR PA view, CT BRAIN plain.ABG analysis were done for patients appropriate to their clinical condition.

The outcome of the patient was analysed by.

1. Length of stay in ICU
2. Need for ventilatory support,
3. Duration of ventilatory support
4. Survival/death
5. APACHE II score

METHOD OF SERUM MAGNESIUM ESTIMATION:

Estimated at Biochemistry Lab in Kilpauk medical college and hospital.

Method – Calmagite Test.

Reagent – Calmagite

Reference range for Magnesium: 1.7- 2.5 mg/dl.

CALMAGITE METHOD:

In an alkaline medium Magnesium binds with calmagite to form a red coloured complex. Interference of proteins and calcium is removed by the addition of detergents and specific chelating agents. The sample containing amount of magnesium is directly proportional to intensity of the colour.

CONTENTS:

L1: Buffer Reagent

L2: Colour Reagent

S: Magnesium Standard

WORKING REAGENT:

For larger assays series a working reagent may be prepared by mixing equal volumes of L1 and L2. This reagent is stable at 2-8 deg C for atleast one month.

PROCEDURE:

Wavelength/filter : 510 nm/green

Temperature : R.T

Light path : 1 cm

CALCULATIONS: Magnesium in mEq/L = Abs.T/Abs.S x 2

ADDITION SEQUENCE	B	S	T
Buffer Reagent	0.5	0.5	0.5
Colour Reagent	0.5	0.5	0.5
Distilled water	0.01	-	-
Magnesium Standard	-	0.01	-
Sample	-	-	0.01

This procedure is linear upto 10mEq/L.If values exceed this limit, dilute the sample with distilled water and repeat the assay. Calculate the value using an appropriate dilution factor.

PRECAUTIONS:

All glassware being used for the test should first be rinsed with 1% or 0.1 N HCl and then with good quality de ionised water before use.

Chelating agents such as EDTA, OXALATE and CITRATE present even in traces, prevent the formation of the colour complex, hence necessary care should be taken during the assay. RBC's have double the magnesium content compared to serum and hence hemolysed samples should not be used.

STATISTICAL ANALYSIS

STATISTICAL TOOL:

Data was analysed statistically by Mean, Standard Deviation, Chisquare test and linear and linear regression. Proportions found using softwares, $p<0.05$ is considered statistically significant.

Independent sample- t test is used to calculate the mean values of the parameters. In this study 95% confidence interval was employed. Tables and Graphs were generated by using Microsoft word and Excel sheet.

Correlation between serum magnesium levels, mortality, need for ventilatory support, duration of ventilatory support, stay in ICU, APACHE score, serum sodium levels, serum potassium levels and serum calcium levels are assessed by chi square test.

SPSS (software package used for statistical analysis) was used for all statistical analysis.

SAMPLE SIZE

It was calculated using the formula $4pq/I^2$

$p=52, q=48$, $I^2=20\%$ of p

$4\times52\times48/ (10.4)^2=92.307$ approx 95

RESULTS:

In our study we analysed 100 patients, in that 53 persons are hypomagnesemics, 47 persons are normomagnesemics

Table 1 AGE DISTRIBUTION AMONG THE STUDY GROUP

Age in years	**No. of cases**	**percentage**
<20	5	5
21-30	14	14
31-40	20	20
41-50	22	22
51-60	14	14
61-70	21	21
>70	4	4
Total	100	100

The minimum age of the patient is <20.The maximum age is >70. Among the 100 patients, 5% are in the age group of <20. 14% are in the age group of 21-30. 20% are in the age group of 31-40. 22% are in the age group of 41-50. 14% are in the age group of 51-60. 21% are in the age group of 61-70. 4% are in the age group of >70.

Figure 1 AGE DISTRIBUTION AMONG STUDY GROUP

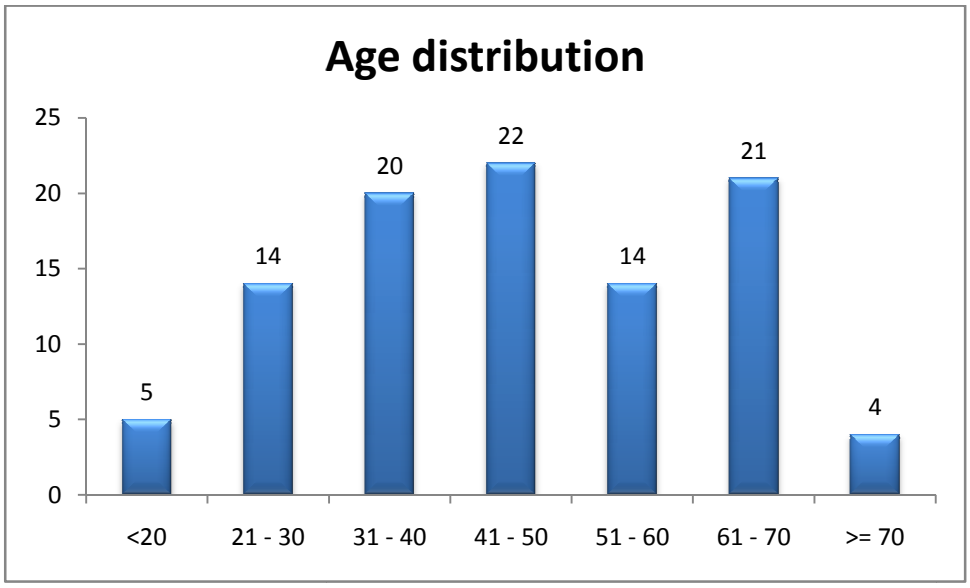


Table 2 MEAN and STANDARD DEVIATION VALUES

	Mean	**Std. Deviation**
AGE	46.96	16.555
S Mg	1.6660	.61401
S Na	136.7600	8.57424
S K	3.7830	.65921
S Ca	9.7360	1.09152
TC	11248.40	4037.585
APACHE II	14.65	7.599
Stay_in_ICU	3.63	1.739

Table 3 GENDER DISTRIBUTION AMONG STUDY POPULATION

Gender	Frequency	Percentage
Male	57	57.0
Female	43	43.0
Total	100	100.0

Among the 100 patients, 57 were males and 43 were females i.e.57% were males and 43% were females.

Figure 2 GENDER DISTRIBUTION AMONG STUDY GROUP

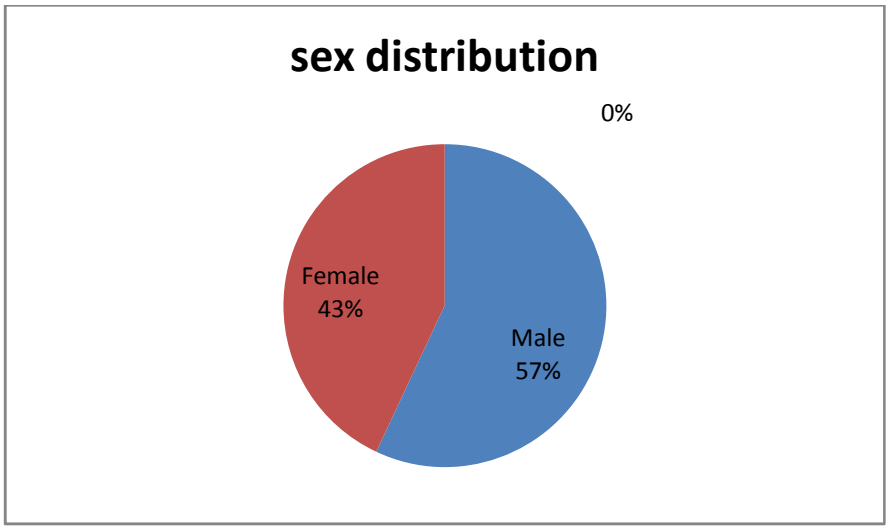


Table 4 DISTRIBUTION OF DIABETES MELLITUS AMONG STUDY GROUP

H/o DM	Frequency	Percentage
Yes	45	45.0
No	55	55.0
Total	100	100.0

Of the 100 patients, 45 are diabetic i.e. 45% are diabetic.

Figure 3 DISTRIBUTION OF DIABETES MELLITUS AMONG STUDY GROUP

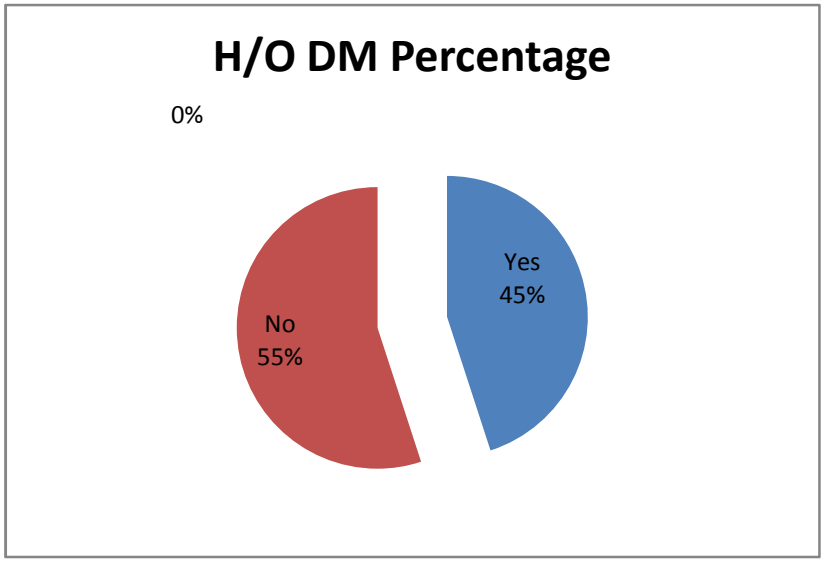


Table 5 HYPERTENSION AMONG STUDY GROUP

H/o HT	Frequency	Percentage
Yes	27	27.0
No	73	73.0
Total	100	100.0

Of the 100 patients, 27 are hypertensive i.e. 27% are hypertensive.

Figure 4 HYPERTENSION AMONG STUDY POPULATION

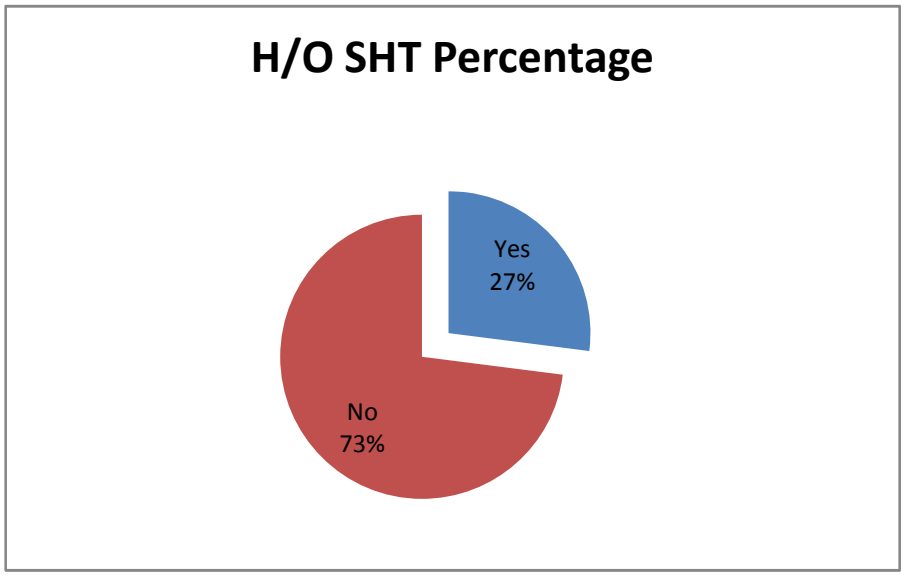


Table 6 ALCOHOLISM AMONG STUDY POPULATION

H/o ALCOHOL	Frequency	Percentage
Yes	19	19.0
No	81	81.0
Total	100	100.0

Of the 100 patients, 19 are alcoholic i.e. 19% are alcoholic.

Figure 5ALCOHOLISM AMONG STUDY POPULATION

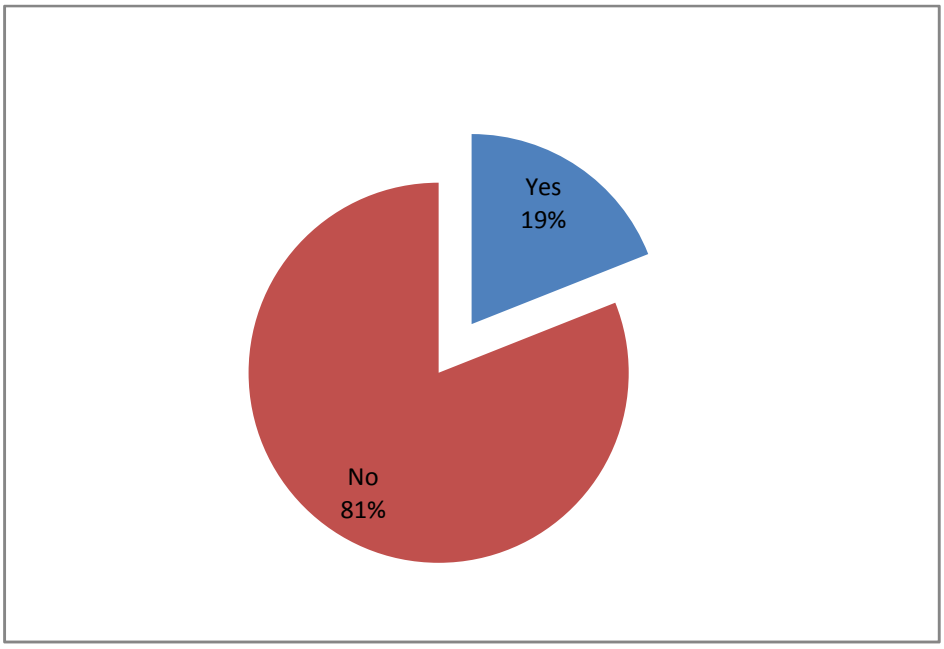


Table 7 CASES AMONG STUDY POPULATION

CASES	Frequency	Percentage
CVA	15	15.0
Heart failure	12	12.0
Poisoning	15	15.0
Respiratory failure	10	10.0
Sepsis	30	30.0
Snake bite	6	6.0
Status epilepticus	5	5.0
DKA	7	7.0
Total	100	100.0

Of the 100 patients, 15% had CVA, 12 % had heart failure, 15% had poisoning , 10% had respiratory failure, 30% had sepsis, 6% had snake bite, 5% had status epilepticus, and 7% had DKA .

Figure 6 CASES AMONG STUDY POPULATION

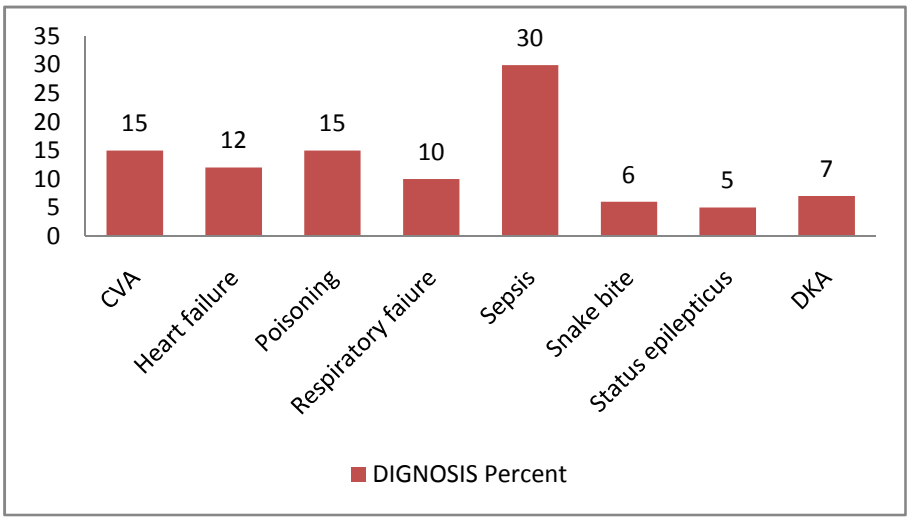


Table 8 DURATION OF HOSPITAL STAY AMONG POPULATION

Duration of stay in days	Frequency	Percentage
1	7	7.0
2	23	23.0
3	20	20.0
4	17	17.0
5	17	17.0
6	12	12.0
8	2	2.0
9	1	1.0
Total	100	100.0

It was noted that 7% of the patients stayed in the ICU for 1 day, 23% for 2 days, 20% for 3 days, 17% for 4 days, 17% for 5 days, 12% for 6 days, 2% for 8 days and 1% for 9 days.

Table 9 REQUIREMENT OF VENTILATORY SUPPORT AMONG STUDY POPULATION

Need for ventilator support	Frequency	Percentage
Yes	24	24.0
No	76	76.0
Total	100	100.0

Of the 100 patients, 24 % required ventilatory support.

Figure 7 VENTILATORY SUPPORT REQIUREMENT AMONG STUDY GROUP

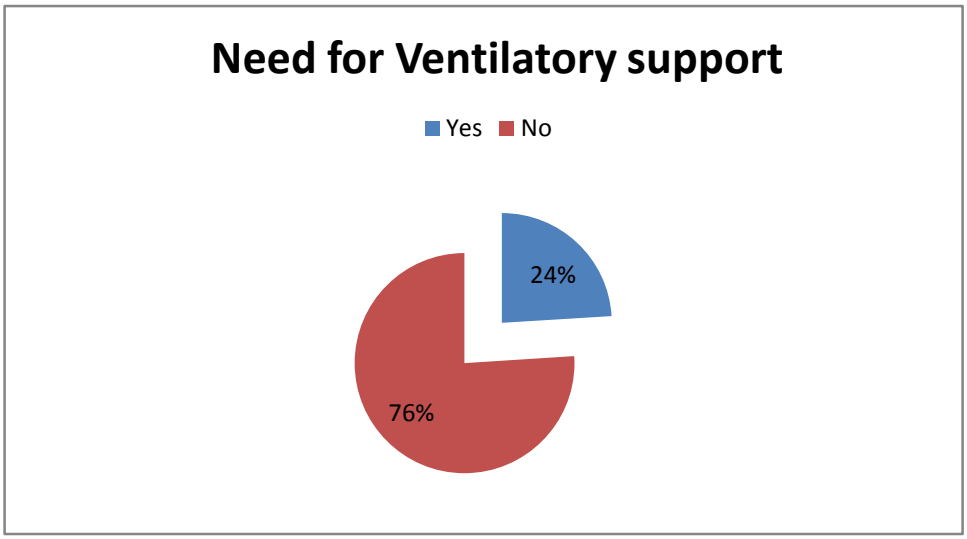


Table 10 DURATION OF THE VENTILATORY SUPPORT AMONG THE STUDY POPULATION

Duration of ventilatory support in days	Frequency	Percentage
1	4	16.7
2	6	25.0
3	8	33.3
4	5	20.8
5	1	4.2
Total	24	100

During the study it was noted that 16.7% of the patients required ventilator support for 1 day, 25% for 2 days, 33.3% for 3 days, 20.8% for 4 days and 4.2% for 5 days.

Table 11 MORTALITY RATES IN THE STUDY POPULATION

Mortality	Frequency	Percentage
Yes	20	20.0
No	80	80.0
Total	100	100.0

Among 100 population, 20% are alive ,80% are died persons

Figure 8 MORTALITY AMONG STUDY POPULATION

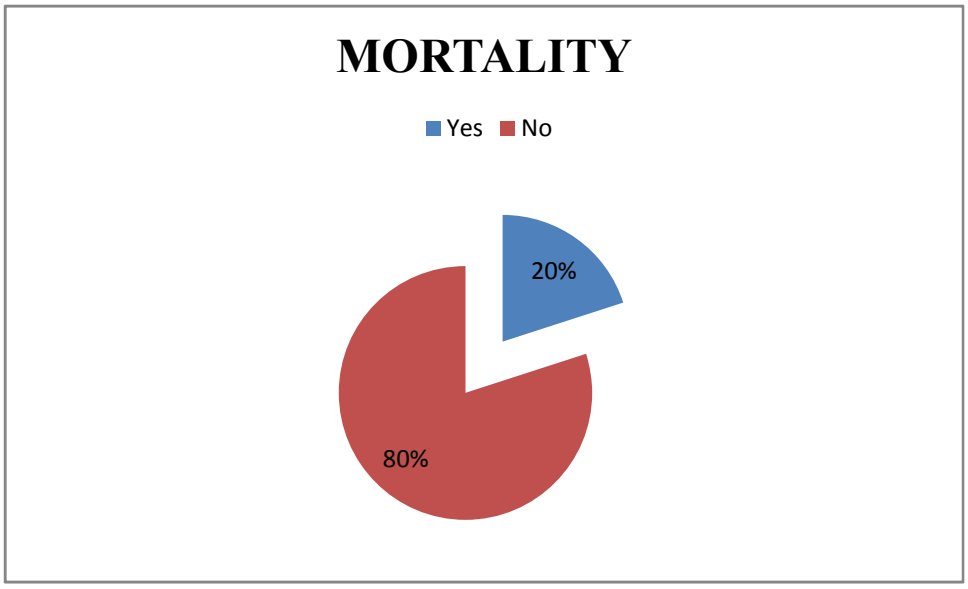


Table 12HYPOMAGNESIMIA AMONG STUDY POPULATION

Hypomagnesemia	Frequency	Percentage
Yes	53	53.0
No	47	47.0
Total	100	100.0

Among the 100 poulation, 53 patients had hypomagnesemia

Figure 9 HYPOMAGNESIMIA AMONG STUDY POPULATION

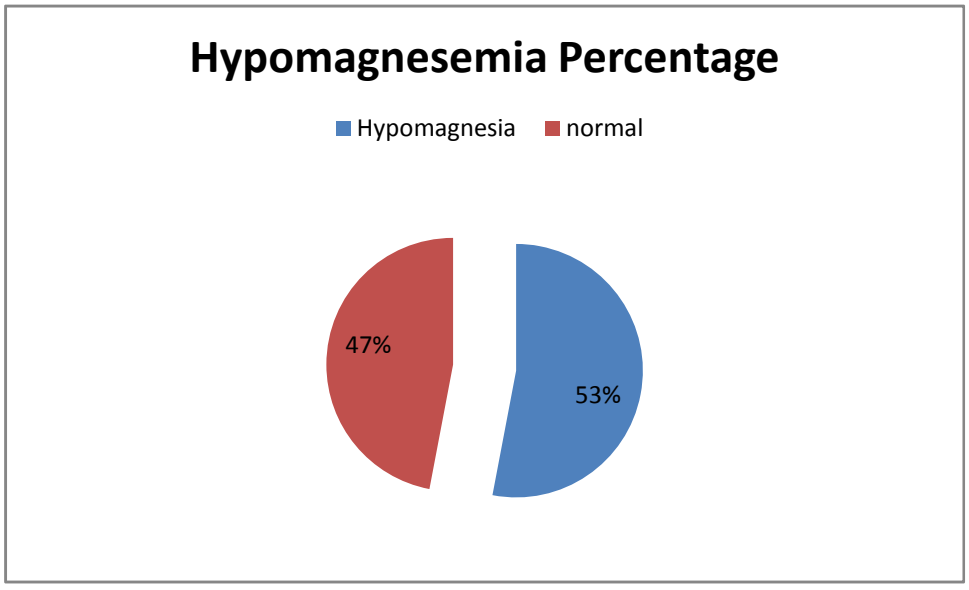


Table 13 HYPONATREMIA AMONG STUDY POPULATION

Hyponatremia	Frequency	Percentage
Yes	33	33.0
No	67	67.0
Total	100	100.0

Among 100 population 33% of patients have hyponatremia, 67% of patients have normal level

Figure 10 HYPONATREMIA AMONG STUDY GROUP

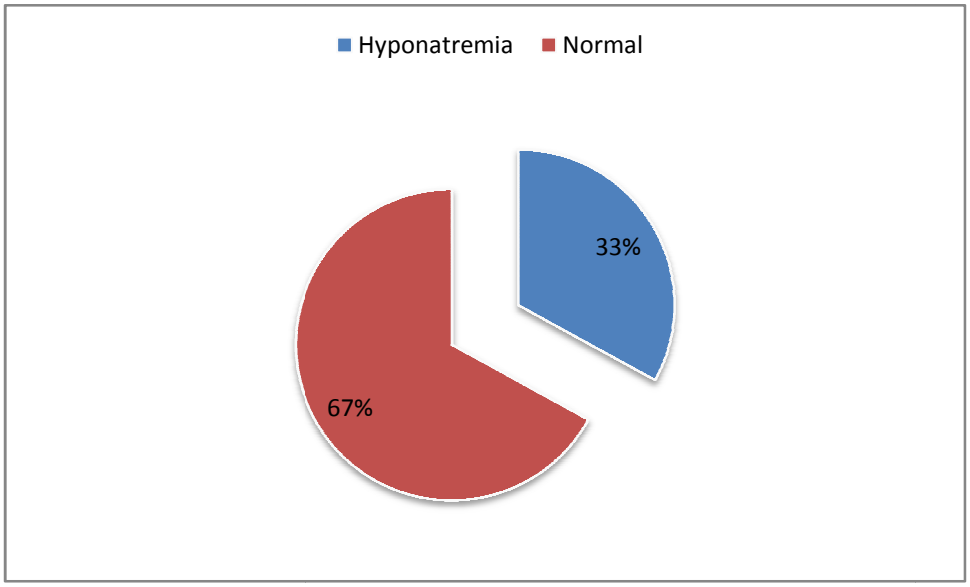


Table 14 HYPOKALEMIA AMONG STUDY POPULATION

Hypokalemia	Frequency	Percentage
Yes	27	27.0
No	73	73.0
Total	100	100.0

Of 100 population 27% are hypokalemic, 73% are normokalemic

Figure 11 HYPOKALEMIA AMONG STUDY POPULATION

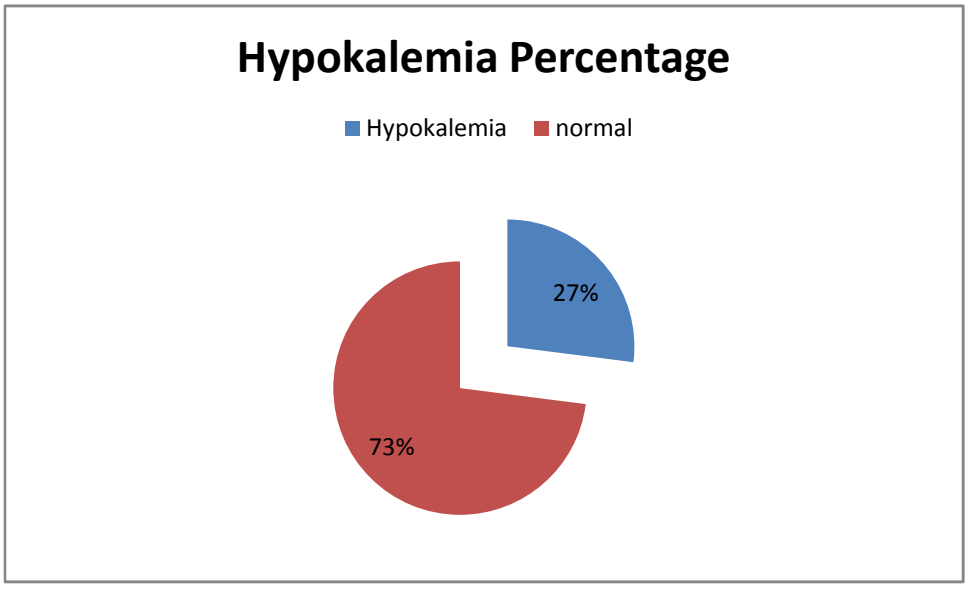


Table 15 HYPOCALCEMIA AMONG STUDY GROUP

Hypocalcemia	Frequency	Percentage
Yes	17	17.0
No	83	83.0
Total	100	100.0

Of 100 population 17% had hypocalcemia, 83% had normal calcium levels

Figure 12 HYPOCALCEMIA AMONG STUDY GROUP

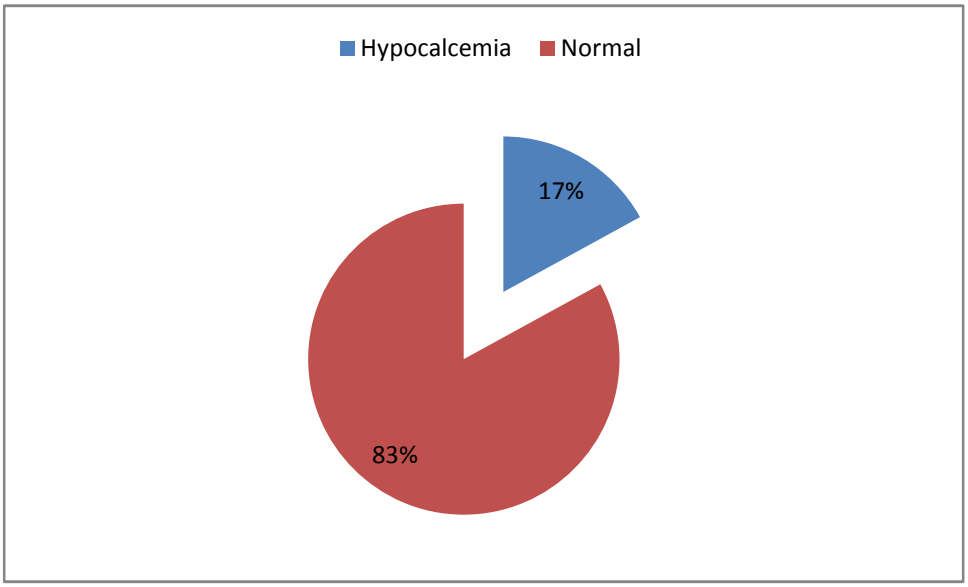


Table 16 APACHE II IN STUDY POPULATION

APACHE II SCORE	Frequency	Percentage
< 4	7	7.0
5 - 9	24	24.0
10 - 14	19	19.0
15 - 19	29	29.0
20 - 24	10	10.0
25 - 29	6	6.0
30 - 34	4	4.0
>35	1	1.0
Total	100	100.0

Among 100 population 7% of patients had APACHE SCORE of 4

24% of patients had APACHE SCORE of 5-9

19% of patients had APACHE SCORE of 10-14

29% of patients had APACHE SCORE of 15-19

10 % of patients had APACHE SCORE of 20-24

6% of patients had APACHE SCORE of 25-29

4% of patients had APACHE SCORE of 30-34

1% of patients had APACHE SCORE of > 35

Figure 13 APACHE II IN STUDY GROUP

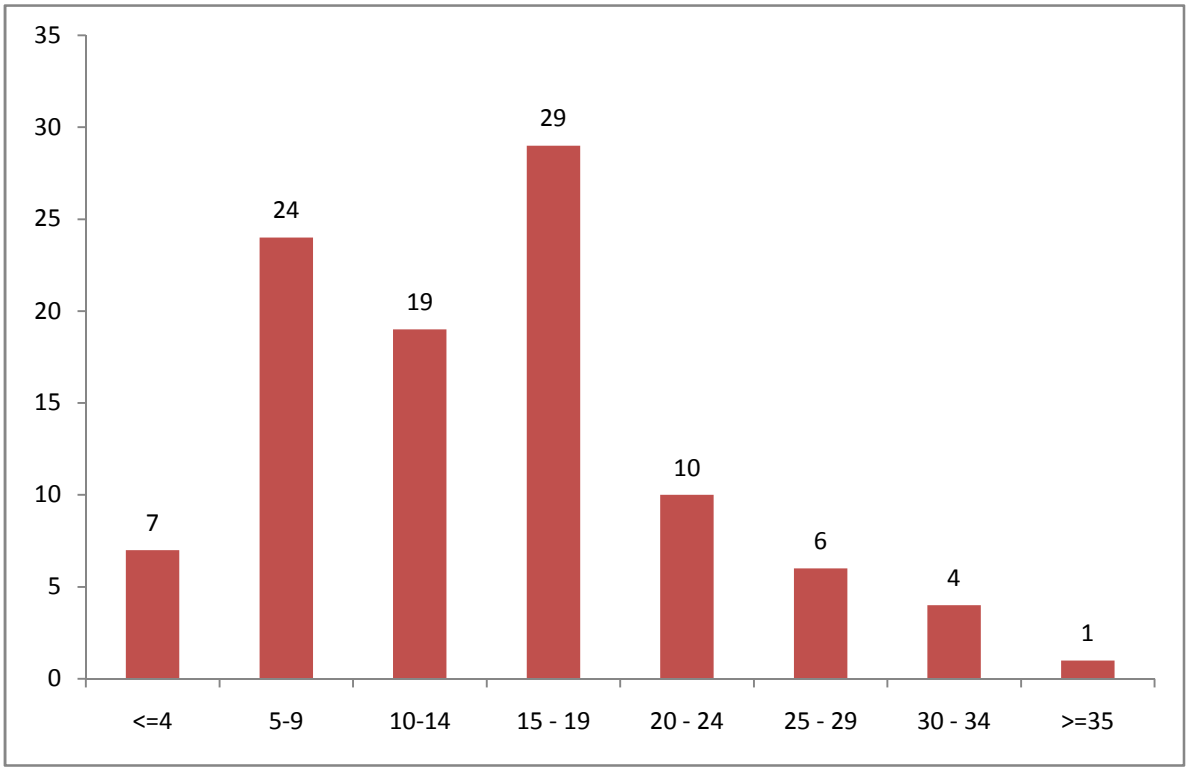


Table 17 STATISTICAL VALUES FOR VARIOUS PARAMETERS

Parameters	Associated hypomagnesemia	Normal magnesium	Chi- square value	P value
DM	25	20	.215	.643
HT	17	10	1.474[a]	.225
ALC	9	10	.299[a]	.585
Hyponatremia	24	9	7.695[a]	.006
Hypokalemia	21	6	9.116[a]	.003
Hypocalcemia	13	4	4.529[a]	.033
Need for ventilator	19	5	8.680[a]	.003
Mortality	16	4	7.316[a]	.007
Duration of ventilator	19	5	4.547	0.337
APACHE-2 score			6.989	0.000
Stay in ICU			19.896	0.011

Table 18 MAGNESIUM LEVELS AMONG VARIOUS AGE GROUP

Age_Group	MAGNESIUM		Total
	Hypomagnesemia	normal	
<20	3	2	5
21 - 30	11	3	14
31 - 40	9	11	20
41 - 50	10	12	22
51 - 60	5	9	14
61 - 70	11	10	21
> 70	4	0	4
Total	53	47	100

In our study we found that maximum number of hypomagnesemia and normomagnesemia were in the age group between 41-50 years.

Minimum age:< 20

Maximum age:> 70

Mean age: 46.51

SD: 18.117

There was no correlation between the age distribution and the Mg levels.

Figure 14 MAGNESIUM LEVELS AMONG VARIOUS AGE GROUPS OF THE STUDY POPULATION

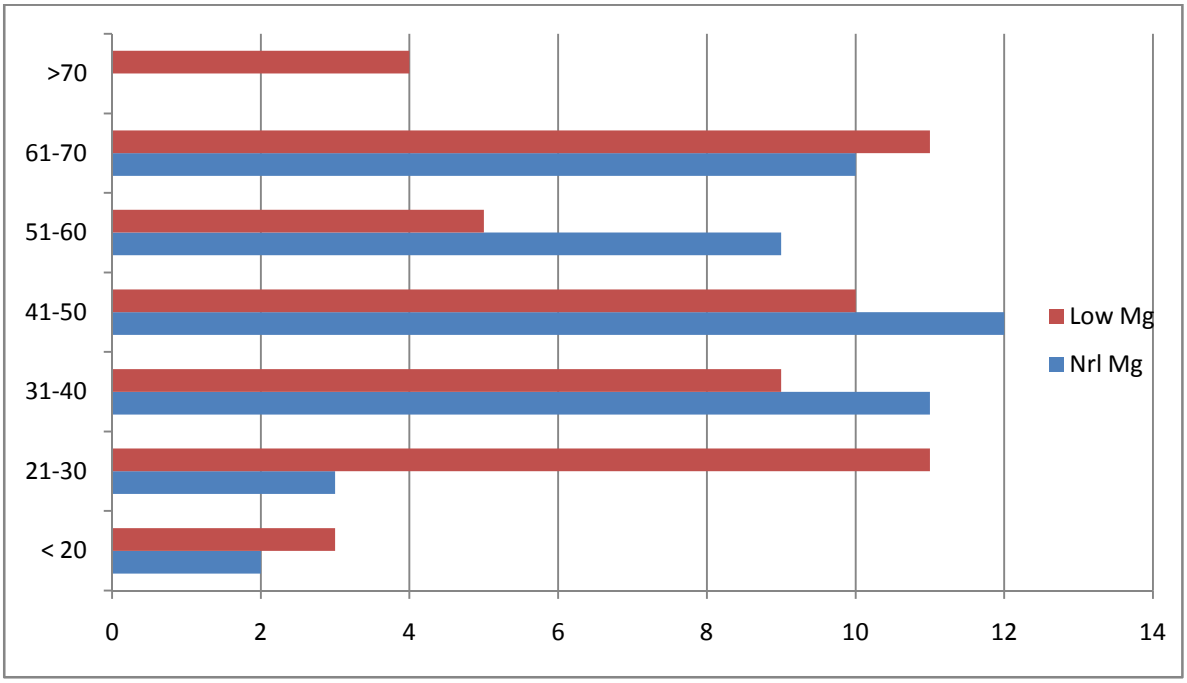


Table 18 GENDERWISE DISTRIBUTION OF MAGNESIUM VALUES

GENDER	MAGNESIUM LEVEL		Total
	Hypomagnesemia	Normal	
Male	32	25	57
Female	21	22	43
Total	53	47	100

Among 100 population, in which 57 were male and 43 were female, it was found that 32 men had hypomagnesemia and 21 female had hypomagnesemia. There was no correlation between sex distribution and Mg levels.

Figure 15 GENDERWISE DISTRIBUTION OF MAGNESIUM VALUES

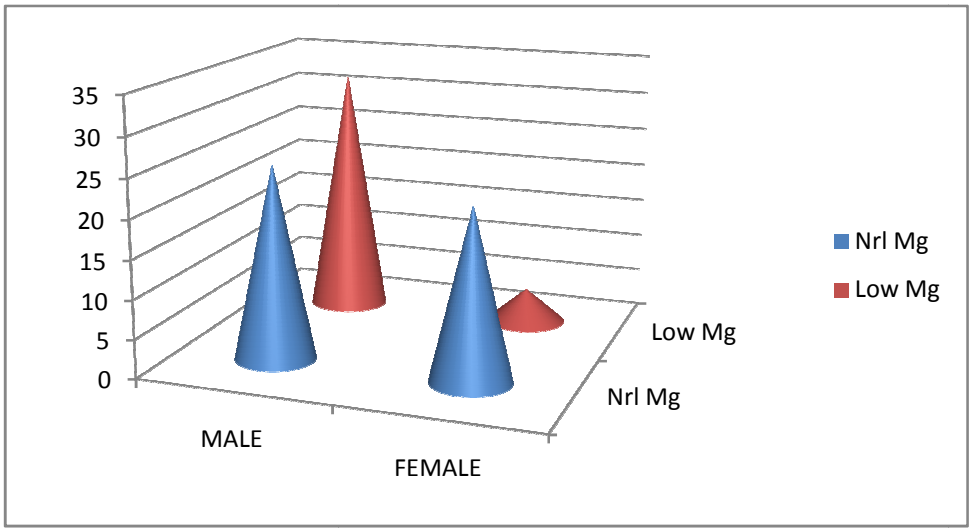


Table 19 MAGNESIUM VALUES AMONG THE VARIOUS SUBGROUPS OF STUDY POPULATION

DISEASES	MAGNESIUM		Total
	Hypomagnesemia	Normal	
CVA	9	6	15
Heart failure	6	6	12
Poisoning	7	8	15
Respiratory faiure	5	5	10
Sepsis	16	14	30
Snake bite	3	3	6
Status epilepticus	3	2	5
DKA	4	3	7
Total	53	47	100

Among 100 population, magnesium levels was found to be low in 16 cases of sepsis ,9 cases of CVA,7 cases of poisoning, ,6 cases of heart failure ,5 cases of respiratory failure, 4 cases of DKA , 3 cases of status epilepticus and 3 cases of snake bite, in this sepsis had more percentage of hypomagnesemic levels.

Figure 16 MAGNESIUM VALUES AMONG VARIOUS SUBGROUPS OF STUDY POPULATION

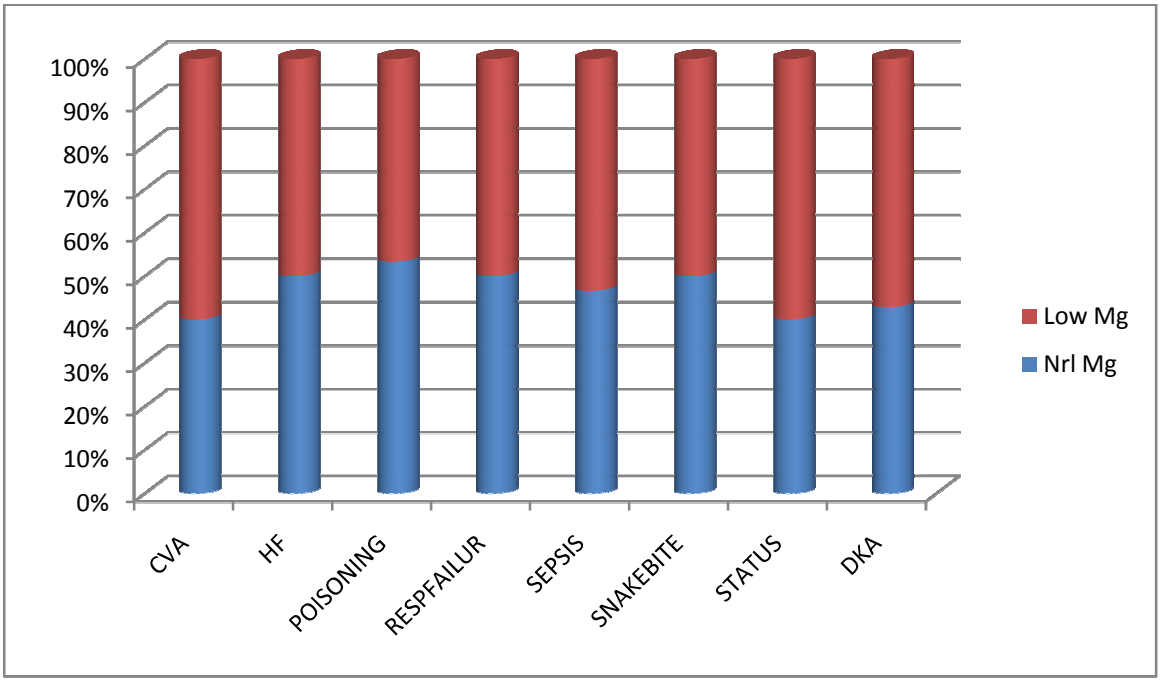


Table 20 ASSOCIATION OF MAGNESIUM LVELS AND DIABETES MELLITUS

		Magnesium		Total	Pearson Chi-Square value	P value
		Hypomagnesemia	normal			
H/O DM	Yes	25	20	45	.215	.643
	No	28	27	55		
Total		53	47	100		

Among the cases, 45 patients had DM, in that 25 patients had hypomagnesemia and 20 patients had normal level of magnesium. P value is 0.643 which is >0.05 so it is not correlated significantly

Figure 17 ASSOCIATION OF MAGNESIUM LEVELS AND DIABETES MELLITUS

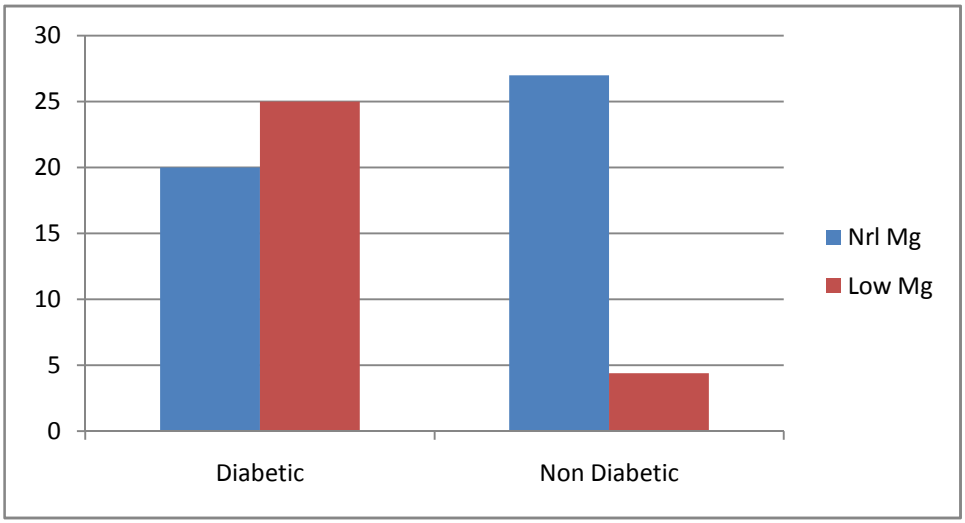


Table 21 ASSOCIATION OF MAGNESIUM LEVELS AND HYPERTENSION

SHT	MAGNESIUM		TOTAL	P-VALUE
	LOW	NORMAL		
YES	17	10	27	0.225
NO	36	37	73	
TOTAL	53	47	100	

Among 100 population, 27% were hypertensives in which 17 patients were found to have hypomagnesemia. Mean value 1.5741.SD-0.49892.P value 0.225 which is > 0.05, so it is not statistically significant

Figure 18 ASSOCIATION OF MAGNESIUM LEVELS AND HYPERTENSION

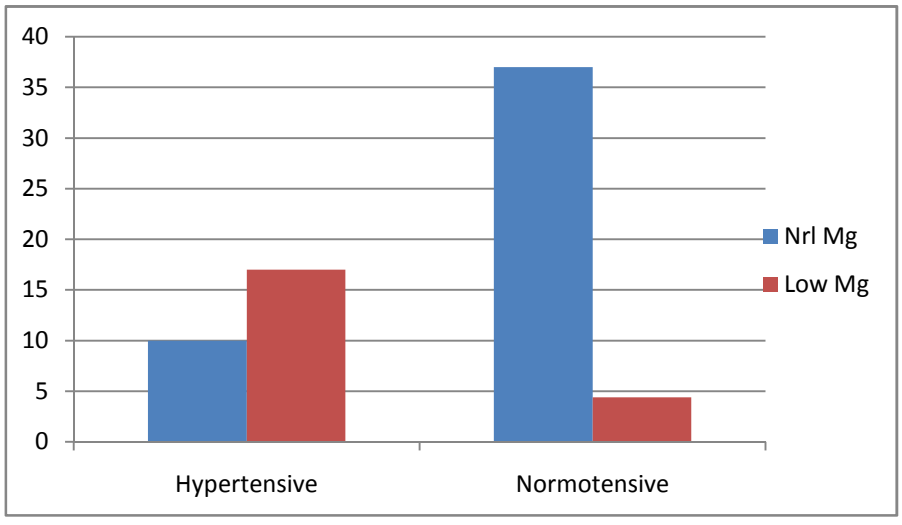
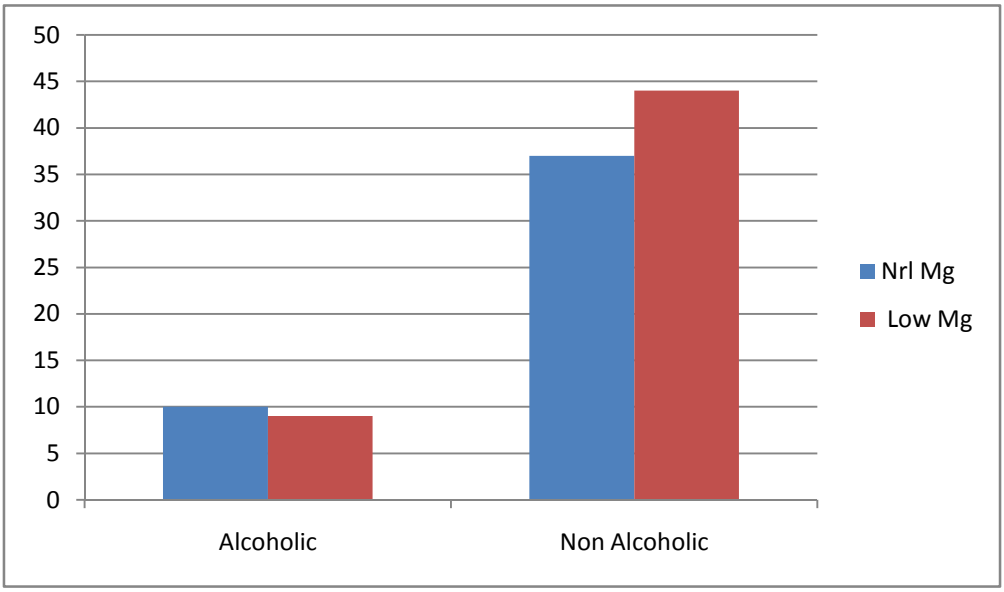


Figure 19 ASSOCIATION OF MAGNESIUM LEVELS AND ALCOHOL

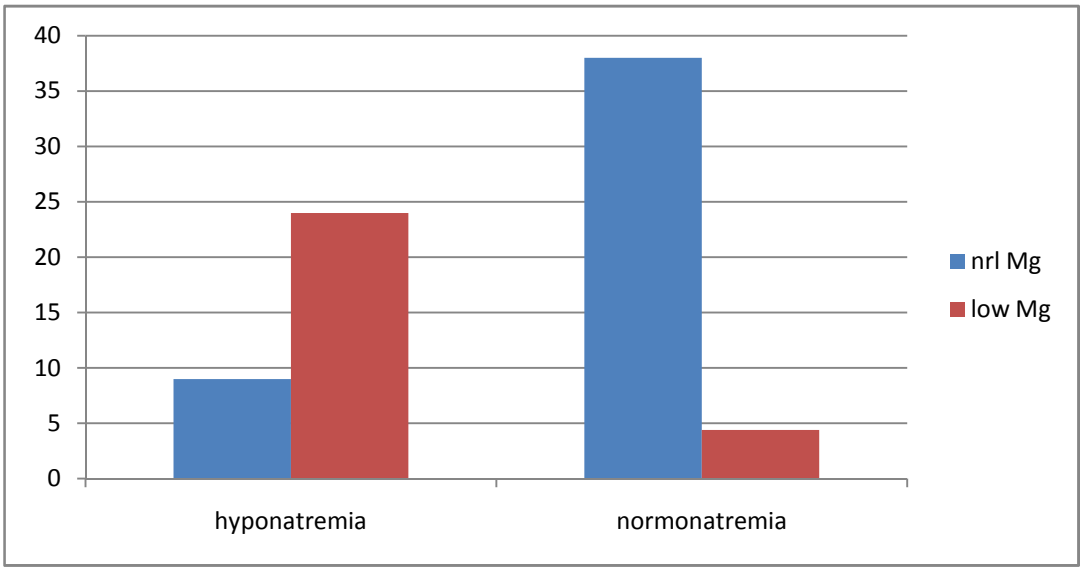


Of 100 patients 19 had alcohol, among that 9 persons had hypomagnesemia. Mean value 1.6632, SD 0.54079, P value 0.585 which is > 0.05 so statistically not significant.

Table 22 ASSOCIATION OF HYPONATREMIA WITH MAGNESIUM LEVELS

SODIUM	MAGNESIUM		Total
	Hypomagnesemia	Normal	
Hyponatremia	24	9	33
Normal	29	38	67
Total	53	47	100

Figure 20 ASSOCIATION OF HYPONATEMIA AND MAGNESIUM LEVELS



Of 100 patients 33 % were hyponatremic, 24 patients had hypomagnesemic. Mean 133.9623, SD 9.39305.P value 0.006 which is <0.05. so statistically significant.

Table 23 ASSOCIATION OF HYPOKALEMIA AND MAGNESIUM LEVLES

POTASSIUM	MAGNESIUM		Total
	Hypomagnesemia	normal	
Hypokalemia	21	6	27
normal	32	41	73
Total	53	47	100

Of 100 patients ,27% had hypokalemia, in that 21 had hypokalemia . mean 3.5434, SD 0.64077,P value 0.003 which is <0.05 so statistically significant

Figure 21 ASSOCIATION OF HYPOKALEMIA AND MAGNESIUM LEVELS

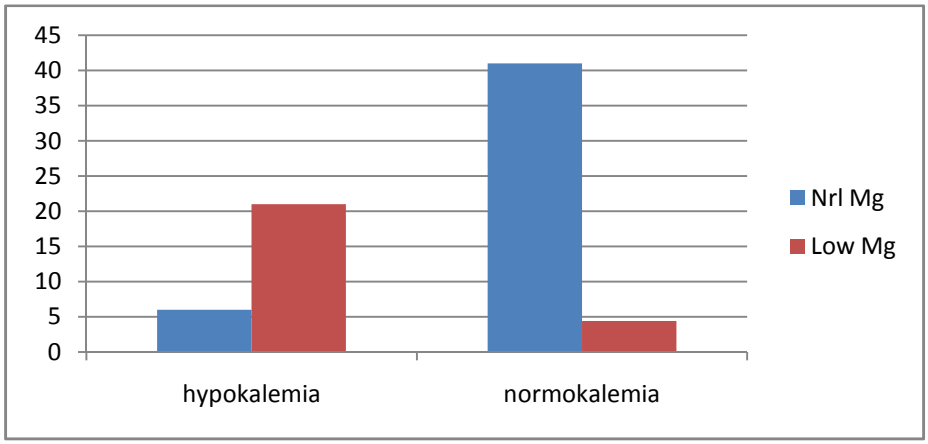


Table 24 ASSOCIATION OF HYPOCALCEMIA AND MAGNESIUM LEVELS

POTASSIUM	MAGNESIUM		Total
	Hypomagnesemia	normal	
Hypocalcemia	13	4	17
Normal	40	43	83
Total	53	47	100

Among 100 patients 17% were hypocalcemia.In that 13 had hypomagnesemia. Mean-9.4623 SD-1.11497 P value0.033 which is <0.05, so it is statistically significant

Figure 22 ASSOCIATION OF HYPOCALCEMIA AND MAGNESIUM LEVELS

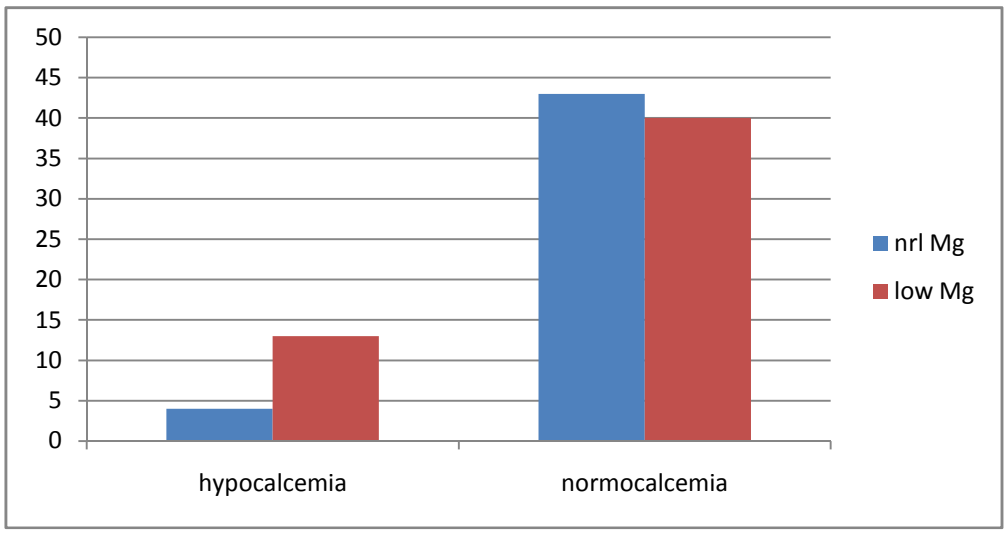


Table 25 ASSOCIATION OF MAGNESIUM LEVELS AND DURATION OF HOSPITAL STAY

STAY IN ICU	**MAGNESIUM**		**Total**
	Hypomagnesemia	normal	
1	4	3	7
2	6	17	23
3	7	13	20
4	10	7	17
5	14	3	17
6	8	4	12
8	2	0	2
9	1	0	1
Total	53	47	100

Among 100 study group mean range of stay in ICU 5, P value is 0.011 which is less than 0.05 so it is statistically significant

Figure 23 ASSOCIATION OF MAGNESIUM LEVLES AND DURATION OF HOSPITAL STAY

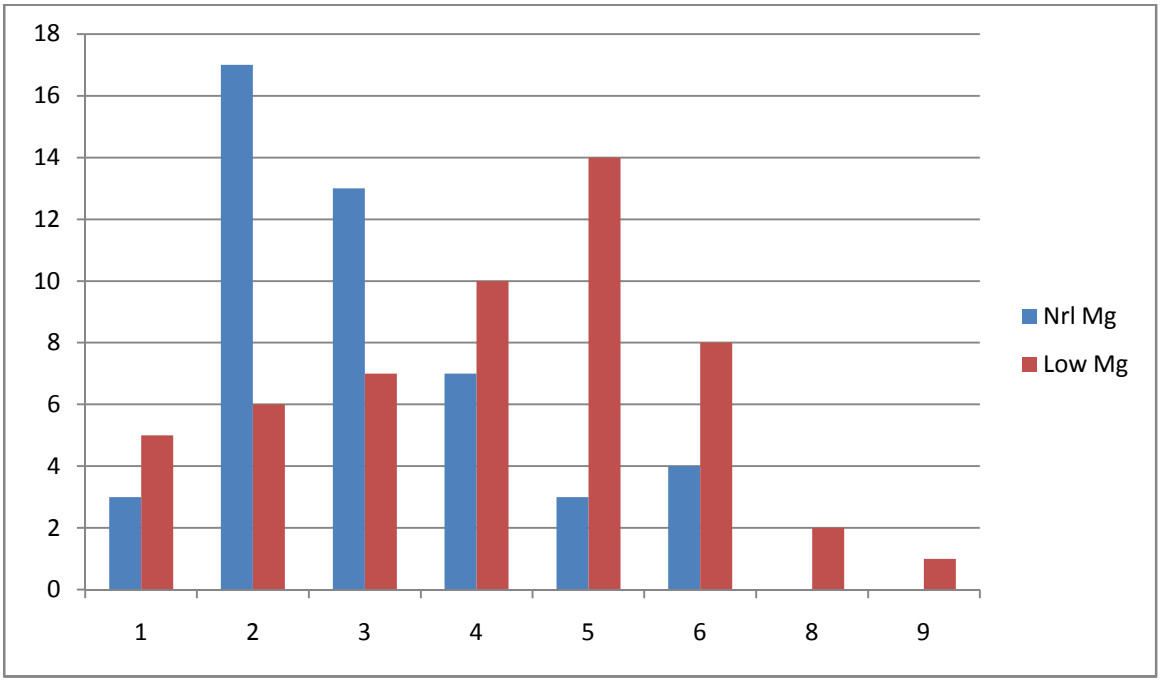


Table 26 ASSOCIATION OF MAGNESIUM LEVELS AND VENTILATORY SUPPORT

N for VS	MAGNESIUM		Total
	Hypomagnesemia	normal	
Yes	19	5	24
No	34	42	76
Total	53	47	100

24 among 100 patients need ventilatory support.in 24 patients 19 had hypomagnesemia. mean value 1.3000, P value 0.003 which is <0.05 so it is statistically significant

Figure 24 ASSOCIATION OF MAGNESIUM LEVELS AND VENTILATORY SUPPORT

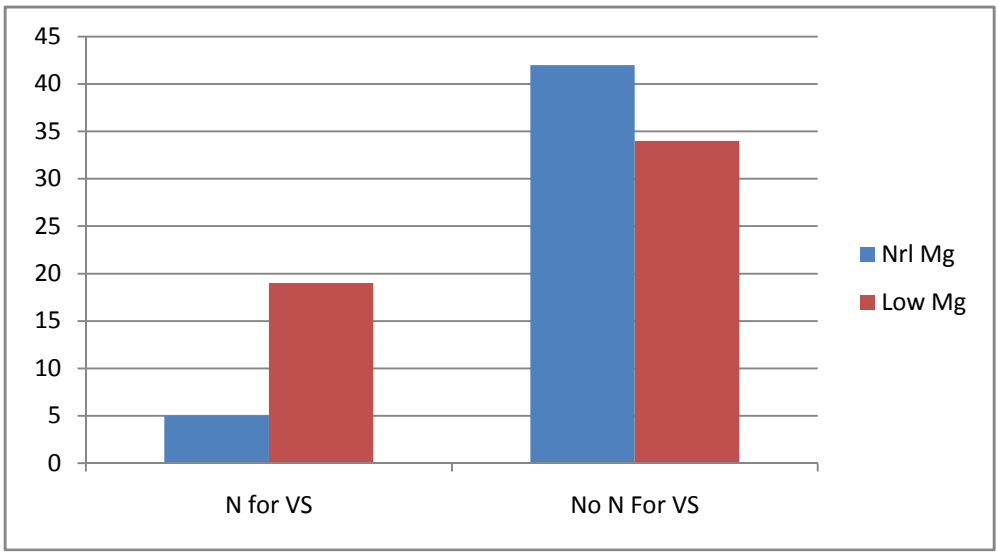
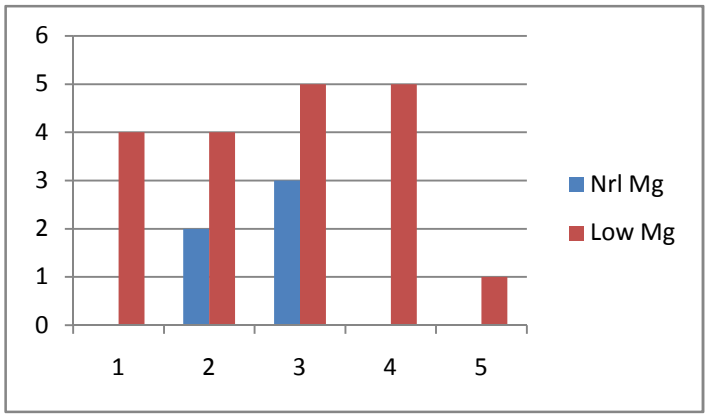


TABLE 27 ASSOCIATION OF MAGNESIUM LEVELS WITH DURATION OF VENTILATORY SUPPORT

DURA.VS	MAGNESIUM		Total
	Hypomagnesemia	normal	
1	4	0	4
2	4	2	6
3	5	3	8
4	5	0	5
5	1	0	1
Total	19	5	24

Figure 25 ASSOCIATION OF MAGNESIUM LEVELS WITH DURATION OF VENTILATORY SUPPORT



P value is 0.337 which is more than 0.05%. Thus there is no significant correlation with duration of ventilatory support.

Table 27 ASSOCIATION OF MAGNESIUM LEVELS WITH MORTALITY

MORTALITY	MAGNESIUM		Total
	Hypomagnesemia	Normal	
Yes	16	4	20
No	37	43	80
Total	53	47	100

Of 100 patients 20 died, out of which 16 had hypomagnesemia. P value 0.007 which is <0.05 so it is statistically significant.

Figure 26 ASSOCIATION OF MAGNESIUM LEVELS WITH MORTALITY

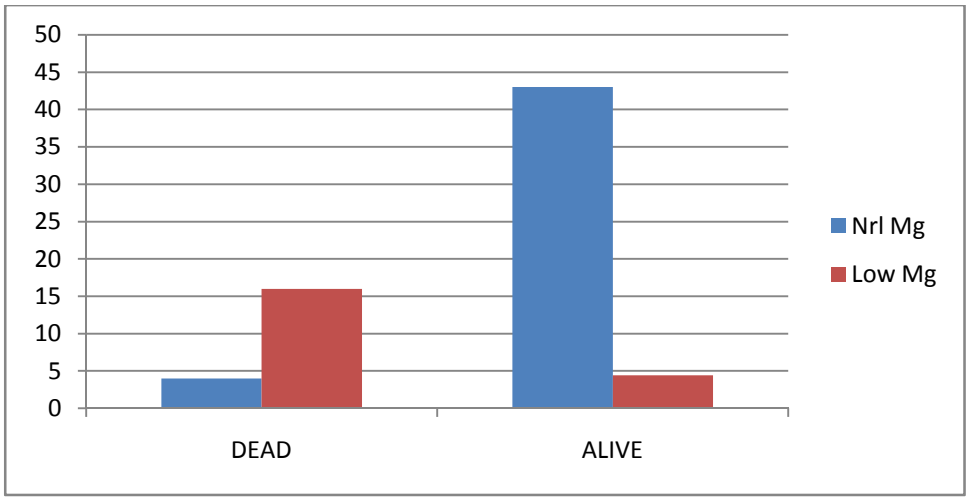


TABLE 28 ASSOCIATION OF MAGNESIUM LEVELS WITH APACHE II SCORE

APACHE II	HYPOMAGNESEMIA	NORMOMAGNESEMIA
>4	0	7
5-9	3	21
10-14	8	11
15-19	25	4
20-24	7	3
25-29	6	0
30-34	3	1
>35	1	0
Total	54	47

Here the significant value is 0.000 which is less than 0.05 which is statistically significant.

Figure 27 ASSOCIATION OF MAGNESIUM LEVELS WITH APACHE II

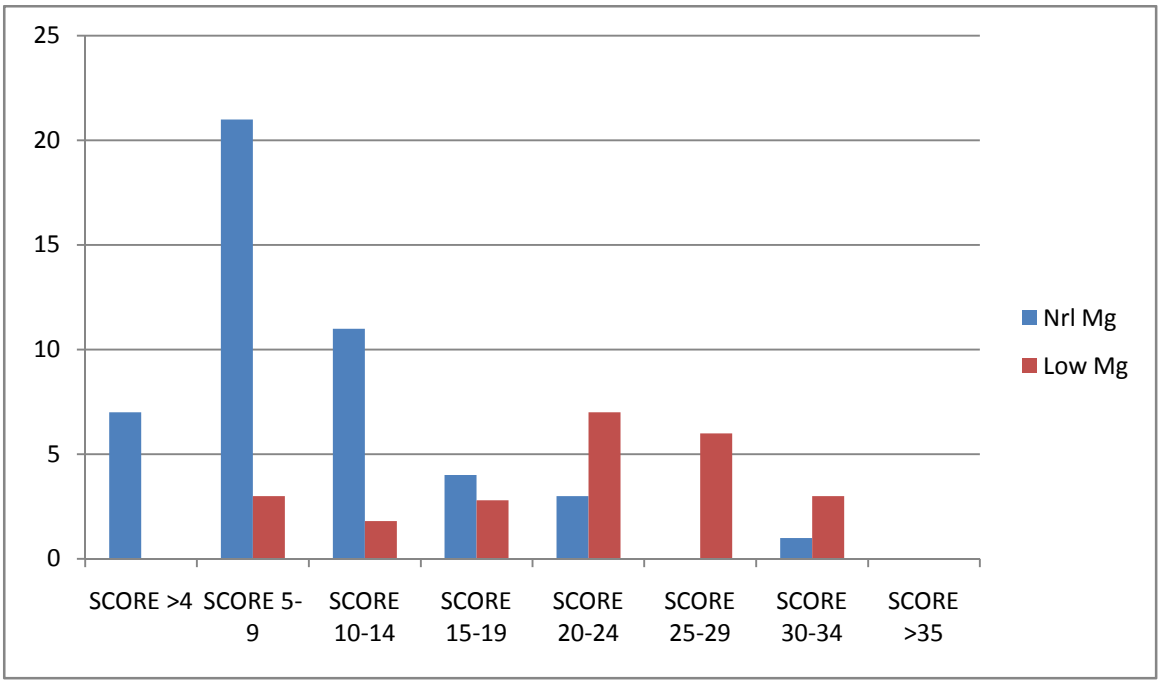


Table 28 MEAN AND STANDARD DEVIATION FOR VARIOUS PARAMETERS AMONG STUDY POPULATION

Group Statistics					
	Hypomagnesemia	N	Mean	Std. Deviation	Std. Error Mean
APACHE II	Hypomagnesia	53	18.70	6.435	.884
	normal	47	10.09	6.107	.891
TC	Hypomagnesia	53	12512.08	4088.421	561.588
	normal	47	9823.40	3503.552	511.046
S K	Hypomagnesia	53	3.5434	.64077	.08802
	normal	47	4.0532	.57478	.08384
S Ca	Hypomagnesia	53	9.4623	1.11497	.15315
	normal	47	10.0447	.98749	.14404
S Na	Hypomagnesia	53	133.9623	9.39305	1.29023
	Normal	47	139.9149	6.26873	.91439

From above results there was no correlation between serum magnesium and diabetes, hypertension, alcohol and duration of ventilator support. There was significant correlation between hypomagnesemia and stay in ICU, need for ventilator support, APACHE II score, Mortality, hyponatremia, hypokalemia and hypocalcemia.

DISCUSSION

Magnesium is a macro mineral. It acts as an essential for life. It is needed by the body in large amounts for many bodily function, like cardiac function, various enzymatic reactions, neuromuscular function, energy production, endocrine function, bone formation and growth, DNA repair and immunity.

Magnesium levels are altered in many conditions like sepsis,inadequate magnesium intake,increased renal loss in case of alcohol abuse, diuretics and digoxin use, and gastrointestinal loss in case of vomiting, diarrhea, nasogastric tube loss, total parenteral nutrition, refeeding with glucose or aminoacids, insulin, metabolic acidosis and hypoalbuminemia , diabetics and acute pancreatitis

Hypomagnesemia leads to muscular weakness, neuromuscular irritability, cardiac arrhythmia, electrolyte disturbances, seizures, and coma

So critically ill patients are at increased risk for hypomagnesemia and development of hypomagnesemia related mortality

In our study, a total of 100 patients were enlisted who were admitted in Intensive medical care unit

We tried to find out prevalence of low serum magnesium level in patients admitted in Intensive medical care unit and association between serum magnesium levels and length of stay, need for ventilator support, duration of ventilator support, APACHE SCORE II, mortality and most predominant illness associated with hypomagnesemia and associated other electrolyte disturbances

In our study, among 100 patients, 53% patients had hypomagnesemia.

Of 100 patients, 32 males had hypomagnesemia and 2 females had hypomagnesemia .

COMPARED WITH OTHER STUDIES

1) Admission hypomagnesemia-impact on mortality or morbidity in critically ill patients done by SAFAVI M[65] middle east J anesthesiol 2007 published in pubmed showed with hypomagnesemia at time of admission had poor prognosis
2) Hypomagnesemia in critically ill medical patients done by LIMAYE CS, published in J association physicians India.2012 May showed patients with hypomagnesemia had higher mortality rate.
3) A higher mortality rate was detected in hypomagnesemia patients as compared to normomagnesemia patients by CHERNOW et al, RUHTEZ et al and SAFAVI et al[64-65]

   In our study number of deaths in hypomagnesemia group was 16, which is significantly higher as compared to 4 patients in normomagnesemia ($p<0.05$)
4) SAFAVI et al- in hypomagnesemia patients the length of ventilator support was increased[65.] But in our study, the correlation between serum magnesium levels and duration of ventilator support was not significant.
5) MUNOZ et al found that the requirement of ventilatory support is higher in patients with low magnesium levels. In our study also found that there was

significant correlation between increased requirement of ventilatory support and hypomagnesemia (p<o.o5)

6) SOLIMAN et al studied that the days of stay in ICU is higher in patients with hypomagnesemia than in normomagnesemic patients. In our present study, hypomagnesemic patients had increased duration of stay in ICU than normomagnesemic, which was significantly correlated with magnesium(p <0.05)

7) WHANG et al and LIMAYE et al studies found hypomagnesemia associated with other electrolyte abnormalities, 42% cases with hypokalemia, with hypophophatemia 29%, with hyponatremia 27%, with hypocalcemia 22%.

In present study showed that there was significant correlation between hypomagnesemia and hyponatremia ,hypokalemia , hypocalcemia .(p <0.05)

8) In a study done by SOLIMAN et al and LIMAYE et al had noted in chronic alcoholic there was one third of patients had hypomagnesemia and LIMAYE et study showed that 24% of alcoholics had hypomagnesemia. In LIMAYE et al study, noted diabetic patients more commonly associated with hypomagnesemia , 27% vs 17%.

In our present study there was no significant correlation between hypomagnesemia and alcoholics,(9 patients had hypomagnesemia in alcoholics vs 10 patients) and diabetes mellitus(P> 0.05)

9) SOLIMAN et al study showed that there was significant correlation between hypomagnesemia and increased APACHE II 11.64 vs 9.5.

In our study had noted that there was significant correlation between hypomagnesemia and increased APACHE II.

10) B.SONTIA, R.M.TOUYZ showed that there was correlation between hypertension and hypomagnesemia.

But in our study , hypertension and hypomagnesemia association is not of much significant.

CONCLUSION

Hypomagnesemia is a common electrolyte imbalance in the critically ill medical patients. It is frequently associated with sepsis. It is associated with higher mortality and morbidity rate in critically ill patients.

Also, hypomagnesemia is associated with increased length of stay and need for ventilatory support .In addition, hypomagnesemia is associated with increased APACHE score. It is associated with hyponatremia, hypokalemia, hypocalcemia.

That is, low magnesium levels in patients admitted in intensive medical care unit may affect the prognosis of patients , hypomagnesemic patients have a guarded prognosis.

Hence in a IMCU set up monitoring of serum magnesium levels along with other electrolytes has a very important therapeutic as well as prognostic implication.

Correction of hypomagnesemia is very essential in the management of critically ill patients to have a better prognosis.

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ANNEXURES

PROFORMA

NAME:

AGE/SEX: I.P.NO.:

OCCUPATION: DATE OF ADMISSION:

ADDRESS:

DIAGNOSIS: DATE OF DISCHARGE:

PAST HISTORY: DIABETES MELLITUS/SYSTEMIC HYPERTENSION

GENERAL EXAMINATION

VITALS:

BP: PR: RR: SPO_2

SYSTEMIC EXAMINATION:

CARDIO VASCULAR SYSTEM

RESPIRATORY SYSTEM

CENTRAL NERVOUS SYSTEM

GLASGOW COMA SCORE

APACHE - II

NEED VENTILATOR:

DURATION OF MECHANICAL VEALNTILATION:

LENGTH OF STAY IN IMCU/HOSPITAL

MORTALITY

INVESTIGATIONS:

COMPLETE HAEMOGRAM

RENAL FUNCTION TEST

SERUM ELECTROLYTES-MAGNESIUM, CALCIUM,POTASSIUM,SODIUM

FBS, PPBS

LIVER FUNCTION TEST

URINE ROUTINE

ECG

CHEST X-RAY

BLOOD CULTURE, URINE CULTURE, CT BRAIN WHEN INDICATED

2D ECHOCARDIOGRAPHY:

ABG ANALYSIS

SIGNATURE OF INVESTIGATOR SIGNATURE OF GUIDE

The APACHE II Severity of Disease Classification System

Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use $A\text{-}aDO_2$ b. $FiO_2 < 0,5$ use PaO_2	a ≥500	350-499	200-349		<200				
	b				> 70	61-70		55-60	<55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)	Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS	Sum of the 12 individual variable points								

B = Age Points

≤44 years	0 points
45-54 years	2 points
55-64 years	3 points
65-74 years	5 points
≥75 years	6 points

C = Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative patients – 5 points

b. For elective postoperative patients – 2 points

APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29)

LIST OF ABBREVIATIONS

Mg Magnesium

APACHE Acute Physiology and Chronic Health Evaluation

TPN Total Parental Nutrition

TRPM Transient Receptor Potential channel Melastatin member

CaSR Calcium Sensing Receptor

ATP Adenosine Triphosphate

PT Proximal Tubule

TAL Thick Ascending Limb

DCT Distal convoluted Tubule

NKCC2 Na+K+2Cl-cotransporter

ROMK Renal Outer Medullary K+

EGF Epidermal Growth Factor

PTH Para Thyroid Hormone

FEV 1 Forced Expiratory Volume – one second

ISIS-4 Fourth International Study of Infarct Survival

ACE Angiotensin Converting Enzyme

H/o Alc history of alcohol intake

N for V S need for ventilator support

Dura. V S duration of ventilator support

S.No	NAME	AGE	SEX	H/ODM	H/OSHT	H/OALC	Diagnosis	S Mg	S Na	S K	S Ca	TC	APACHE II	STAY IN ICU	N for VS	DURA VS	MORTALITY		
1	Raniammal	78	F	yes	no	no	Sepsis	1	136	3.8	9.4	16500	25	3	yes	3	yes		
2	Yasodha	70	F	no	no	no	Sepsis	2	126	4	10	14600	20	6	no	nil	no		
3	Rajalingam	50	M	no	no	no	Status epilepticus	2.1	140	4.2	10.4	12000	14	2	no	nil	no		
4	Murugan	55	M	no	no	yes	Heart failure	1	126	3	10	15600	10	4	no	nil	no		
5	Ethiraj	38	M	no	no	yes	Poisoning	2	140	4.2	10.6	8000	18	4	no	nil	no		
6	Angalan	65	M	yes	no	yes	CVA	1	126	3	9	11400	18	5	no	nil	no		
7	Murugan	45	M	yes	no	yes	Sepsis	2	126	4	10	14600	10	3	no	nil	no		
8	Kanniammal	48	F	yes	no	no	DKA	1.1	145	3.1	10	11400	15	5	no	nil	no		
9	Mohammed abbas	50	M	yes	yes	yes	Heart failure	2	136	4	11	9800	7	1	no	nil	no		
10	Annamalai	40	M	no	no	no	Respiratory failure	0.8	132	2.5	9	16700	18	5	yes	3	no		
11	Valli	31	F	no	no	no	Respiratory failure	2	146	4	10.5	7600	6	2	no	nil	no		
12	Subramani	40	M	yes	yes	yes	sepsis	1	142	4.3	11	9240	5	3	no	nil	no		
13	Mohan	28	M	no	no	no	sepsis	1.1	138	3.8	9.4	8400	8	3	no	nil	no		
14	Arumugam	43	M	no	no	no	Respiratory failure	2.4	140	3.8	10	11000	8	2	no	nil	no		
15	Mohandoss	48	M	no	no	yes	Heart failure	2.2	146	4	9.8	7600	5	2	no	nil	no		
16	Mohabul begam	48	F	no	yes	no	Status epilepticus	2.4	138	4.2	8.6	9900	9	2	no	nil	no		
17	Veeriya Perumal	69	M	yes	no	no	CVA	1.3	142	4.2	8.8	7200	5	0	no	nil	no		
18	Gajendran	70	M	yes	yes	yes	Respiratory failure	2	146	4	11	9800	9	2	no	nil	no		
19	Palanisamy	60	M	no	yes	no	Heart failure	2	138	4	10	8600	9	1	no	nil	no		
20	Subburaj	40	M	no	yes	no	CVA	1.1	112	3	10	13400	14	6	no	nil	no		
21	Raji	40	M	no	no	no	Status epilepticus	1.2	128	3	7.8	14400	18	5	yes	3	no		
22	Kothandaraman	65	M	no	yes	no	CVA	2.4	126	2.5	10	13200	24	4	no	nil	no		
23	Rosaiya	43	M	yes	no	no	Sepsis	1.1	112	2.5	8.6	18500	24	5	yes	4	yes		
24	Srinivasan	65	M	yes	no	no	CVA	2	148	5	10	9200	14	1	no	nil	no		
25	Prakasam	49	M	yes	yes	no	CVA	1.3	135	4	10	10300	20	8	no	nil	no		
26	Loganadhan	55	M	yes	no	yes	Sepsis	2.4	144	3.6	9.4	3000	11	4	yes	3	no		
27	Vairamani	55	M	no	yes	no	Heart failure	1.1	126	3.5	9	13400	32	4	yes	4	yes		
28	Umarani	39	F	yes	yes	no	Heart failure	1	135	3.5	8	15600	28	2	yes	2	yes		
29	Narendran	23	M	no	yes	no	Status epilepticus	1.3	140	4	10	13200	18	4	no	nil	no		
30	Jubaitha	67	M	yes	yes	no	CVA	2.1	132	2.4	11	4800	6	4	no	nil	no		
31	Radha	65	F	no	no	no	Respiratory failure	2.3	136	4	11	11400	8	3	no	nil	no		
32	Manjula	29	F	no	yes	no	Status epilepticus	1.2	130	3.6	9.6	11200	20	4	no	nil	no		
33	Rani	68	F	yes	no	no	CVA	1.4	140	4	11	9600	18	5	no	nil	no		
34	Kumar	52	M	yes	yes	yes	Respiratory failure	1	126	3.5	10	15400	30	6	yes	4	yes		
35	Arunchunaiselvi	16	F	no	no	no	sepsis	0.9	128	3.2	9.2	13500	34	6	yes	4	yes		
36	Krishnan	17	M	yes	no	no	sepsis	1.2	142	4.2	10.6	6700	14	3	no	nil	no		
37	Duraisamy	70	M	yes	yes	no	Sepsis	1.3	140	4	11	18600	18	6	no	nil	no		
38	Natrajan	52	M	no	no	no	sepsis	2.1	144	3.9	8.4	11000	6	3	no	nil	no		
39	Sivagami	85	F	yes	yes	no	Heart failure	1.2	136	3.5	9	12600	36	1	yes	1	yes		
40	Santhakumar	19	M	yes	no	yes	Sepsis	2.5	144	4.4	11	14800	14	4	no	nil	no		
41	Sathish	26	M	no	no	no	sepsis	0.8	126	4.5	10.8	12600	16	6	no	nil	no		
42	Kuppammal	42	F	yes	yes	no	Heart failure	2.2	145	4	10	8600	8	3	no	nil	no		
43	Ponni	65	F	no	no	no	CVA	1.2	126	3	9	14500	20	1	no	nil	yes		
44	Saranya	20	F	no	no	no	sepsis	2	146	3.8	9.8	8600	11	2	no	nil	no		
45	Ganapathy	65	F	yes	yes	no	CVA	2.4	144	4.6	9.9	10200	3	2	no	nil	no		
46	Sivalingam	24	M	yes	yes	no	Snake bite	1.2	140	3.6	9.6	13800	16	3	no	nil	no		
47	Poomima	21	F	no	no	no	Poisoning	2.2	138	4	10	12400	5	2	no	nil	no		
48	Manjunadhan	25	M	no	no	no	Poisoning	1.1	140	4	9.6	9600	18	5	no	nil	no		
49	Nagaraj	45	M	yes	no	yes	Poisoning	1.3	145	4.5	10.6	12400	16	5	no	no	no		
50	Chinnaponnu	35	F	no	no	no	Respiratory failure	2.5	145	4	10	8700	8	2	no	nil	no		

51	Saroja	65	F	yes	no	no	CVA	2	138	3.6	9.1	7800	9	3	no	nil	no			
52	Arul	33	M	yes	yes	yes	DKA	1.2	146	2.8	8.1	10800	18	4	no	nil	no			
53	Munivel	30	M	no	no	no	Poisoning	1	132	3.9	11.2	9300	28	4	yes	2	yes			
54	Appavu	71	M	no	no	no	Sepsis	1	126	3	8	16700	18	5	yes	3	no			
55	Rajendran	48	M	no	no	no	Sepsis	2	134	3.8	9.8	16200	32	6	yes	3	yes			
56	Manojkumar	23	M	yes	no	no	DKA	1.1	140	3	9.6	10800	14	4	no	nil	no			
57	Sezhiyan	43	M	no	no	yes	Sepsis	2	145	4.5	10	4500	6	4	no	no	no			
58	Devi	30	F	yes	no	no	DKA	1.3	141	3.1	8.8	12000	15	5	no	nil	no			
59	Malliga	50	F	yes	no	no	DKA	2.4	142	2.9	11	11400	4	3	no	nil	no			
60	Santhi	53	F	yes	yes	no	Heart failure	2	145	4	9.8	8900	10	2	no	nil	no			
61	Kuberthiran	50	M	no	no	yes	sepsis	1.2	116	3	8.2	2700	18	2	yes	2	yes			
62	Krishnaveni	65	F	yes	yes	no	Heart failure	1.5	145	4	11	8000	16	6	no	nil	no			
63	Eswaran	65	M	Yes	no	no	CVA	1.1	130	2	7	12400	24	2	yes	2	yes			
64	Venugopal	42	M	yes	no	no	Poisoning	1.2	141	4.1	9.4	8800	14	9	no	nil	no			
65	Meraka	63	F	yes	yes	no	Poisoning	1.4	140	5	10.4	10000	14	8	no	nil	no			
66	Padma	47	F	yes	no	no	Sepsis	1.2	132	3	8	22300	18	5	yes	4	no			
67	Chandrasekar	51	F	no	yes	no	Heart failure	1.2	126	3	11	12400	18	4	no	nil	no			
68	Gowri	35	F	no	no	no	Heart failure	3	145	4.5	10	7600	10	2	no	nil	no			
69	Sekar	50	M	no	no	no	CVA	1	142	4	10	13400	25	2	no	nil	yes			
70	Valli	50	F	no	no	no	Respiratory failure	1.2	140	3.6	9	13200	26	1	yes	1	yes			
71	Ganapathy	58	M	no	no	yes	sepsis	2.4	135	4	10	3600	11	3	no	nil	no			
72	Anjalacchi	43	F	yes	no	no	Sepsis	1.1	114	3	8	23600	18	6	yes	5	yes			
73	Maduraiveeran	32	M	no	no	no	Poisoning	1.1	128	3.8	11	12000	22	5	no	nil	no			
74	Elumalai	70	M	no	no	no	Poisoning	2.1	144	4.4	9.4	9100	4	3	no	nil	no			
75	Seraiya	20	F	no	no	no	Poisoning	1.3	142	4.6	8.4	9600	16	4	no	nil	no			
76	Saraswathy	21	F	no	no	no	Poisoning	2.4	146	4.5	10	6900	18	3	no	nil	no			
77	Lalitha	65	F	no	no	no	Respiratory failure	1	126	2.5	7	16700	27	2	yes	1	yes			
78	Jaganathan naidu	60	M	yes	no	yes	Sepsis	1.8	144	3.4	8.8	15500	4	5	no	nil	no			
79	Poongodiammal	70	F	no	no	no	Sepsis	0.8	112	2.5	8	18900	26	1	yes	yes	yes			
80	Dhanasekar	26	M	no	no	no	Snake bite	1.1	148	3.2	9	9000	16	4	no	nil	no			
81	Anjali	40	F	no	yes	no	Respiratory failure	1.3	145	4	11	12400	16	5	yes	3	no			
82	Dhanabakkiyam	82	F	no	yes	no	CVA	1.4	138	4	10	14500	18	6	no	nil	no			
83	Raja	35	M	no	no	no	Sepsis	1.9	128	4.2	10	16400	8	6	yes	3	no			
84	Shanthi	33	F	no	no	no	Sepsis	2.3	146	4.8	11	14500	6	5	no	nil	yes			
85	Rani	65	F	no	no	no	Poisoning	2.5	145	4.6	10	7000	8	2	no	nil	no			
86	Sathyamoorthy	47	M	yes	no	no	CVA	2.3	140	3.8	8.6	6400	4	2	no	nil	no			
87	Rajeswari	60	F	yes	no	no	DKA	2.3	138	3.3	10.8	9000	4	3	no	nil	no			
88	Dhatchayani	70	F	no	no	no	sepsis	1.2	136	3.5	10	4700	11	3	no	nil	nil			
89	Chandra	50	F	no	no	no	Poisoning	2.4	128	4.5	8	12600	22	4	yes	2	yes			
90	Vijayakumar	27	M	no	no	no	Snake bite	0.8	140	4.4	8.4	13000	12	2	no	nil	no			
91	Sureshkumar	52	M	no	no	yes	Sepsis	1.4	140	4	11	4600	18	3	no	nil	no			
92	Kasthuri	36	F	no	no	no	Poisoning	1.9	138	4.2	9	8900	18	3	no	nil	no			
93	Manoj	38	M	yes	no	no	DKA	2.3	144	3.2	11	11400	18	3	no	nil	no			
94	Durai	34	M	yes	no	yes	Sepsis	1.2	140	4	10	15600	16	5	no	nil	no			
95	Gopalakrishnan	40	M	yes	no	no	Sepsis	2	142	4.6	8.8	16900	11	5	no	nil	no			
96	Sarala	34	F	no	no	no	Snake bite	2.2	144	3.8	14	10400	6	2	no	nil	no			
97	Selvi	54	F	yes	no	no	Snake bite	2	138	5.2	8.8	8800	12	2	no	nil	no			
98	Ammaniammal	58	F	yes	yes	no	Sepsis	2.3	128	5	11	2800	4	6	yes	2	yes			
99	Sasikumar	32	M	no	no	no	Poisoning	2.1	146	4.6	9.8	9900	6	3	no	nil	no			
100	Gopi	22	M	yes	no	no	Snake bite	2.3	139	4.5	11	5800	6	2	no	nil	no			

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Ref.No.2212/ME-1/Ethics/2014 Dt:03.04.2014.

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on Serum magnesium level and effect on mortality and morbidity in patients admitted in intensive medical care unit" – For Project Work submitted by Dr.Sumathira M, MD (GM), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
31 MAY 2014
Kilpauk, Chennai-10.

CHAIRMAN, 30/5/14.
Ethical Committee
Govt.Kilpauk Medical College,Chennai